Direct Arylations of Azoles

A thesis presented for the degree of

DOCTOR OF PHILOSOPHY IN

ORGANIC CHEMISTRY

by

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Chapter 3. Towards the Total Synthesis of Mechercharmycin A

Abbreviations

Bipy	2,2-bipyridine
Cy	cyclohexyl
CuTc	copper (I) thiophene-2-carboxylate
DAST	diethylaminosulphur trifluoride
dba	dibenzylidenacetone
DBU	1,8-diazabicyclo(5.4.0)undec-7-ene
dppb	diphenylphosphinobutane
dppe	diphenylphosphinoethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dpph	diphenylphosphinohexane
dppm	diphenylphosphinomethane
dppp	diphenylphosphinopentane
DCM	dichloromethane
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethyl propylene urea
DMSO	dimethylsulfoxide
equiv	equivalent(s)
h/hrs	hour(s)
HBP	Hermann-Beller palladacycle

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Im	imidazole
IMes	1,3-bis(mesityl)imidazol-2-ylidene
LC-MS	liquid chromatography-mass spectrometry
NBS	*N*-bromosuccinimide
NMP	*N*-methyl-2-pyrrolidione
PEPPSI-iPr	[1,3-Bis(2,6-Diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Py	pyridine
R.T.	room temperature
TBAF	tetrabutylammonium fluoride
TIPS	triisopropylsilyl
THF	tetrahydrofuran
TFAA	trifluoroacetic anhydride
TBDPS	*t*-butyldiphenylsilyl
X-PHOS	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Preface

Parts of this thesis have been communicated in the literature and have been co-written by the author of this thesis:

"Direct Arylations On Water: Synthesis of 2,5-Disubstituted Oxazoles Balsoxin and Texaline" Ohnmacht, S.A., Mamone, P., Culshaw, A.J., Greaney, M.F. *Chem. Comm.* **2008**, 1241-1243.

"Direct Arylations of 2*H*-Indazoles On Water" Ohnmacht, S.A., Culshaw, A.J., Greaney, M.F. *Org.Lett.* **2010**, 12, 224-226.

Acknowledgements

Firstly I would like to thank my supervisor Dr. Michael F. Greaney for giving me the opportunity to conduct this research in his laboratories. I would like to thank him for his advice, guidance and support over the last three years as well as his continuous support of my ideas and superb theoretical input on any problems I faced him with. I would like to thank everyone in the Greaney group, especially Dr. E. Ferrer-Flegeau, Dr. K. Meyer, Dr. J. Smith, Dr. Aileen Mitchell, Didier Pintori and Venu Bhat as well as all the guys who supported my research in any way, namely John Millar, Raymond Borwick, Alan Taylor, Marika de Cremoux, Juraj Bella, Tim Calder and Annette Burgess. Thanks also to everyone in the Greaney group, past and present. I also would like to thank the University of Edinburgh and the School of Chemistry for providing the facilities, the Swansea EPSRC National Mass Spectrometry Service Centre at the University of Wales for analytical data as well as Novartis UK and the EC for funding (Novartis CASE award and Marie Curie scholarship).

I would also like to extend my thank you to lab 38B14 at Novartis in Horsham, where I had the joy and privilege to work for 3-months alongside my brilliant co-supervisor Dr. A. Culshaw, Dr. L. Sharp, Dave Beattie, Ryan West, Dr. C. Thompson as well as Dr. D. Sandham.

Finally I would like to thank the most special people in my life - my mom, the best mom in the world - Walter, the coolest, smartest and best cooking man I know - my dear brother Felix who doesn't cook as good but will be an outstanding professor one day - and last but not least my loving, caring and gorgeous fiancé Jennifer, who had to put up with me during the time I wrote this thesis while finishing medical school herself. This is for all four of you, thank you for being part of my life and making me happy every day. Thank you!

Stephan A. Ohnmacht

Dedication

Diese Doktorarbeit widme ich voller Stolz meiner liebevollen, einzigartigen und unersetzbaren Mama. So viele Jahre schon stehst du felsenfest an meiner Seite und begleitest mich durch mein Leben. Es ist unglaublich schoen zu wissen dass es zu Hause jemanden gibt der an allem was man unternimmt, Interesse zeigt.

Fuer dieses Interesse und so unglaublich viele andere Dinge danke ich dir von ganzem Herzen. Bleib so wie du bist und geniesse das pensionierten Leben, du hast es dir mehr als verdient.

In Liebe und mit immenser Hochachtung davor, dass du uns zwei lange alleine und mit so viel Energie, Gleichberechtigung und Liebe grossgezogen hast.

Dein gluecklicher und stolzer Sohn,

Stephan

Abstract

This thesis is divided into three main chapters. A general introduction including the results from the successful direct arylation of oxazoles forms the first chapter. The second chapter highlights our results of the useful direct arylation of 2*H*-indazoles, which was developed using our previously identified conditions. Finally, the third chapter describes our efforts towards the total synthesis of the cyclic polyoxazole natural product, mechercharmycin A.

The functionalisation of heteroaromatic compounds by transition metal (TM) catalysed C-C bond formation complements classic condensation chemistry as a strategy for poly-functional heteroaromatic synthesis. Whereas classic heterocyclic synthesis frequently involves the preparation of appropriately substituted acyclic precursors which undergo cyclo-condensation as a final step, TM-catalysed cross couplings offer the possibility of taking the parent, commercially available heteroarenes and selectively functionalising the C-H bonds around the heteroarene nucleus. Whilst the condensation route is generally reliable and built upon many years of literature precedent, the preparation of the appropriately substituted precursor is necessarily multi-step and the subsequent condensation is usually carried out under forcing conditions. The TM-catalysed approach offers significant advantages of speed and synthetic expediency in comparison, along with the potential for mild C-C bond forming reaction conditions.

Importantly, the cross-coupling route enables the introduction of diversity at a late stage, rather than the early stage mandated by the condensation approach, a strategic advantage in the type of intensive analog synthesis required by contemporary medicinal and agrochemical chemistry.

The TM-catalysed approach becomes even more attractive if direct arylation can be incorporated as a C-C bond forming reaction. Here, the stoichiometric metallation required for classic cross-couplings such as the Suzuki-Miyaura, Stille and Negishi reactions is dispensed with, in favour of direct C-H bond functionalisation. Reported in this thesis is the preparation of assorted 2,5-diaryloxazoles as well as 2,3-diarylindazoles using TM-catalysed chemistry. The

oxazole and indazole heteroarene structures have widespread application in medicinal, agrochemical, natural products and materials chemistry.

We have taken our methodology further and subsequently investigated the potential of direct arylations on oxazoles, targeting challenging molecules such as mechercharmycin A, a cytotoxic natural product.

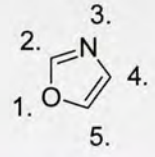
Chapter 1.

General Introduction and Direct Arylation of Oxazoles

1.1 Introduction

1.1.1 Oxazole

Oxazole is a five membered π-electron excessive aromatic heterocyclic compound with a nitrogen atom in the 3-position and an oxygen atom in the 1-position (Figure 1). The 2-position of oxazole is partially electropositive due to the electronegativity of the neighbouring heteroatoms making it the most acidic (pKa ~20) in the molecule, followed by the 5-position and least acidic, the 4-position. The 5-position in addition, is reactive towards electrophilic substitution reactions as it is very electron rich.[1] It was over 100 years ago that the first oxazole has been reported, the oxazole literature has since then continuously grown and oxazole related publications can now be found in many areas of chemistry such as medicinal chemistry, materials science as well as natural products.[2-5] Oxazole itself is a liquid at room temperature and has a boiling point of 69°C.



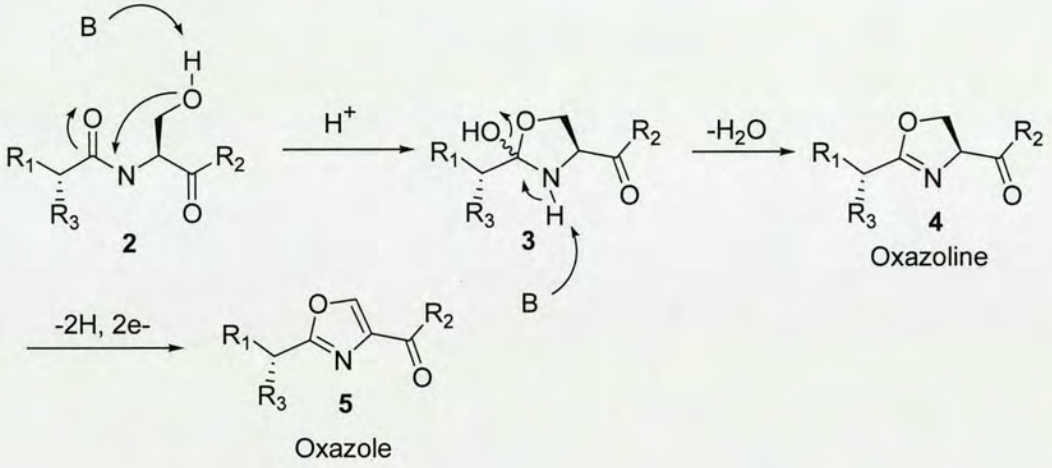
1

Figure 1. 1,3-Oxazole and its numbering.[1]

Naturally occurring oxazoles used to be considered very rare until about 20 years ago, when several natural products such as the calyculins, hennoxazoles and ulapualides were isolated from marine organisms.[6] In nature, oxazoles are assembled using either a serine or a threonine moiety as the key structural motif for biosynthesis (Scheme 1).[7] Examples of this biosynthesis include microcin, epothilone D (both thiazole) and sulfomycins I-III (oxazole).[8-10]

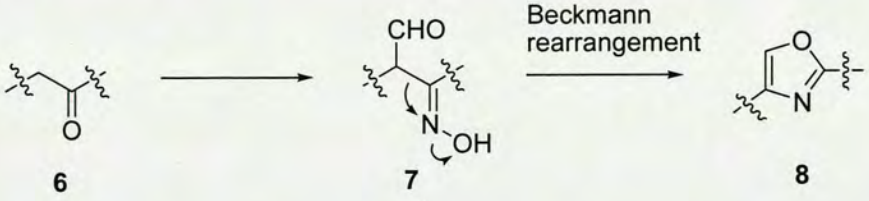
The lone pair of a base such as histamine abstracts the hydrogen on the acidic hydroxyl group, which in turn then attacks the carbonyl carbon of the peptide moiety in an intramolecular fashion (Scheme 1). A second removal of a hydrogen atom, this time on the nitrogen of the previously formed 5-membered ring, ultimately eliminates water from the reaction. The then formed intermediate undergoes an

enzymatic oxidation to generate the oxazole, substituted at the 2- and 4-positions. In the case of threonine the 5-position is substituted with a methyl group, in the case of serine it remains vacant. Oxazole is a weak base with a pKa of 0.8 (conjugate acid), compared to a pKa of 7 for imidazole.[1]



Scheme 1. The *in vivo* pathway (ribosomal) to generate oxazoles.[7]

In addition to the amino acid biosynthetic pathway there has been an increasing amount of data suggesting a possible non-ribosomal (non-amino acid) biosynthetic pathway in the biosynthesis of marine derived oxazoles. Uemura *et al.* have investigated a possible Beckmann rearrangement of α,β-unsaturated oximes or α-formyl ketoximines.[11]



Scheme 2. Possible non-amino acid pathway for the biosynthesis of marine derived oxazoles.[11]

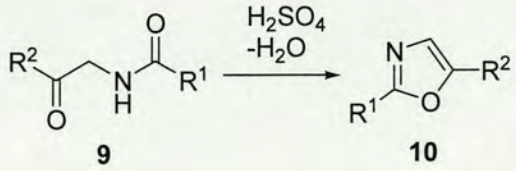
In 2005 the group was able to publish a Beckmann rearrangement using cyclododecanone. Treatment of the ketone with trimethyl orthoformate and

$BF_3.OEt_2$, followed by oxime formation gave α-formyl ketoximine dimethyl acetal. Heating this compound with PPA in toluene afforded the oxazole in an excellent yield.[11] A one-step procedure was also developed but showed a significant drop in isolated yields of the corresponding oxazole. Several other oxazole analogues have been synthesised in this manner; this research provided the first experimental results to support the non-amino acid pathway of oxazoles. Investigations into the elucidation of this biogenesis of oxazoles remain an interesting topic. We have yet to fully understand and experimentally prove that this approach is indeed possible in nature.[11]

Spectroscopically, oxazole and its analogues have characteristic resonances in the ^1H NMR as well as the ^{13}C NMR. 1,3-Oxazole itself resonates between 7.00 ppm and 8.00 ppm in the proton spectrum. Substituents on one of the three carbons can produce chemical shifts of up to a full ppm. Resonances in the carbon spectrum are typically in the aromatic region ranging from 125.4 ppm for C4 in the unsubstituted 1,3-oxazole up to 161.1 ppm for C2 with a sulfur substituent ($S-CH_3$) attached.[2] The parent 1,3-oxazole also shows absorbances in the IR and UV analysis has its λ_{max} at 205 nm in methanol. Oxazoles continue, after more than a century, to be of great interest in synthetic chemistry.

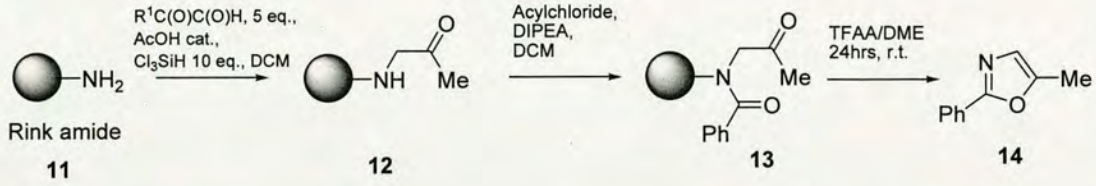
1.1.2 Synthesis of Oxazoles

Many different approaches to synthesise oxazoles have been communicated in the past and present literature. The decision of which approach is chosen for a synthesis depends highly on the desired substitution pattern of the target oxazole compound. One of the earliest syntheses of 2,5-disubstituted oxazoles is the Robinson-Gabriel synthesis. The Robinson-Gabriel method is the reaction of 2-acylamino-ketones to oxazoles via a dehydration in acidic medium. Generally concentrated sulphuric acid can be used as a dehydrating agent but phosphorus-oxychloride has been shown to have similar effects. The 2-acylamino-ketones utilised in this transformation can be obtained via the Dakin-West reaction.[12-14]



Scheme 3. The Robinson-Gabriel synthesis of oxazoles.[12]

A more recent application of the Robinson-Gabriel synthesis by Pulici *et al.* sees the use of solid-supported resins in combination with trifluoroacetic anhydride to generate functionalised oxazoles.[15]



Scheme 4. Trifluoroacetic anhydride-mediated solid-phase version of the Robinson Gabriel synthesis of oxazoles.[15]

Early procedures to generate oxazoles also included the oxidation of oxazolines. Nickel peroxide has been shown to be an efficient reagent for the oxidation of activated oxazolines containing an electron-withdrawing group, such as esters for example.[16] The NiO_2 method was originally reported by Meyers and Evans and still to this day, remains one of the most widely used methods to generate oxazoles, even with the advent of other, newer methodologies.[17] The oxidation of oxazolines to oxazoles is a heterogeneous process in which the starting material is refluxed in benzene with excess of NiO_2. This methodology was used in the synthesis of eupolauramine and provided the oxazole product **16** from an inactivated oxazoline **15** in a modest 55 % isolated yield.[18] In addition to NiO_2, other oxidants can be used to generate oxazoles. Reagents such as MnO_2 and copper salts such as $CuBr_2$ have been shown to promote the formation of oxazole with high efficiencies.[19-25] Table 1

highlights several reactions and conditions used to generate substituted oxazoles from oxazoline precursors.

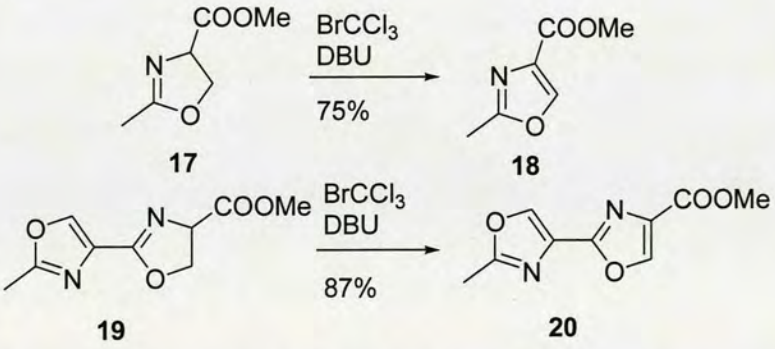
Table 1. Oxidation of oxazolines to oxazoles.

15 **16**

Entry	R^1	R^2	R^3	Yield (%)
i)	C_6H_5	CH_2CN	4-CH_3S-C_6H_4	54[a]
ii)	C_6H_5	$CH_2OCOC_6H_5$	4-CH_3S-C_6H_4	40[a]
iii)	C_6H_5	CO_2Me	H	55[b]
iv)	C_6H_5CH=CH	CO_2Me	H	61[b]
v)	*i*Pr	CO_2Me	H	76[c]
vi)	C-C_6H_{11}	CO_2Me	H	66[c]

a = $CuBr_2$ / LiBr / $CaCO_3$, b = nickel peroxide, c = NBS

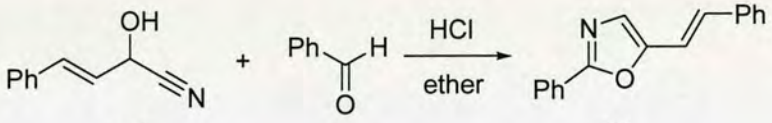
Further, $BrCCl_3$ / DBU has been reported to oxidise oxazolines in a similar fashion. This reaction does not involve a metal-based oxidation, but works via halogenation of the oxazoline followed by a dehydrohalogenation to give an overall net oxidation. Williams *et al.* have used this method with high efficiency in their attempt to generate bis-oxazoles.[26]



17 **18** **19** **20**

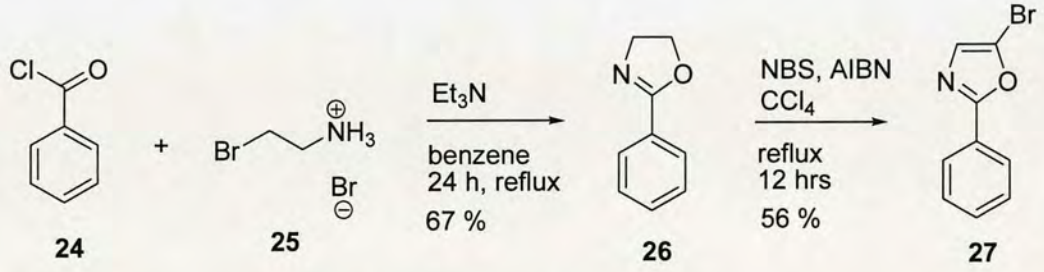
Scheme 5. Use of $BrCCl_3$ in the oxidation of oxazolines to oxazoles.[26]

Another strong and highly mentionable classic synthesis of oxazoles is the Fischer synthesis of oxazoles, developed by Fischer *et al.* in 1896.[27] The reaction involves the use of an aldehyde and cyanohydrins in acidic medium (anhydrous HCl) and ether as solvent. This approach is another one-step condensation reaction, complementary to the Robinson-Gabriel approach to generate 2,5-disubstituted oxazoles (Scheme 6).[27,28]



Scheme 6. Fischer synthesis of oxazoles using hydrochloric acid in ether.[27,28]

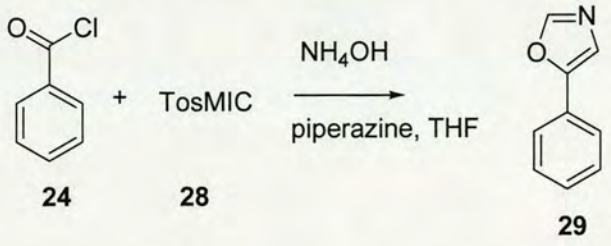
An approach via a condensation of an aromatic acid chloride with 2-bromoethylamine hydrobromide in benzene utilising five equivalents of triethylamine followed by treatment of the intermediate with N-bromosuccinamide (NBS), carbon tetrachloride and azabisisobutyronitrile (AIBN) seems very feasible if the five position is to be substituted. With this approach, the 4-position of the oxazole remains vacant for possible further modifications.[29]



Scheme 7. Two step oxazole formation.[29]

There are also more modern, and sometimes higher yielding TosMIC (toluenesulphonylmethyl isocyanides) reactions to be found in the literature.[30] This method, developed by the Dutch chemist van Leusen, involves the use of an aldehyde (such as benzaldehyde, or any other substituted benzaldehyde analogue), which is treated with ammonium hydroxide, piperazine and THF to generate imines,

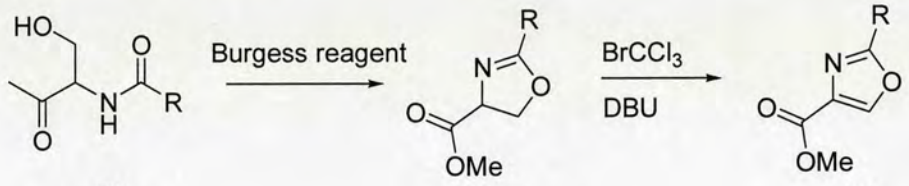
which give oxazoles substituted at the 5-position in high yields (see results and discussion for more details on this reaction).[31]



24 **28** **29**

Scheme 8. Reaction using TosMIC to generate 5-substituted oxazole.[30,31]

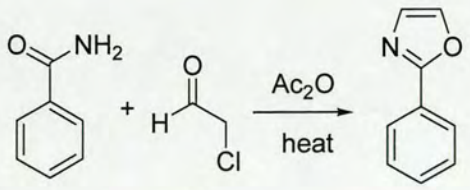
Another very broadly applied pathway to oxazoles is the synthesis from peptide precursors. Scheme 9 shows the two-step synthesis of a 2,4-disubstituted oxazole via dehydration (in this case using Burgess' reagent), followed by the oxidation of the obtained intermediate using $BrCCl_3$ and DBU as the base.[32]



30 **31** **32**

Scheme 9. Two step procedure to form 2,4-disubstituted oxazoles.[32]

Another classical condensation approach to form the oxazole framework is a modification of the well-known Robinson-Gabriel synthesis.[33] The Hantzsch oxazole synthesis employs a benzamide (with varying substitutents on the aromatic ring to generate diversity for the starting materials) as well as chloro-acetaldehyde (highly toxic), acetic anhydride and in addition, elevated temperatures. Yields for these classic condensation transformations are generally found to range from 30 % up to a maximum of 60 % due to polymer formation and the extreme reactivity of the chloroacetaldehyde.



33 **34** **35**

Scheme 10. Synthesis of 2-aryl substituted oxazoles via condensation reaction.[33]

For further examples and a list of several other miscellaneous methods to generate oxazoles up to the year 2003, refer to Palmer's book on oxazoles in reference 2, part A, chapter one.[2]

1.1.3 Oxazoles in Natural Products

Over the last two decades several oxazole containing natural products have been isolated and many of these isolated natural products show interesting biological activities such as antitumor, peripheral analgesic, antibacterial, antileukemic, antifungal as well as antiviral activities.[34-36] The general interest in oxazoles and therefore also in the functionalisation of these compounds has increased immensely and more synthetic efforts have been directed towards oxazole containing natural products in recent years.[37,38] A review highlighting recent advances in the total syntheses of oxazole containing natural products has been published and provides an excellent overview.[39] Given the availability of this thorough review, we will focus solely on the structures of the oxazole containing natural products and will highlight the key step involving the oxazole core for the selected synthesis.

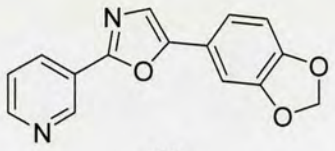


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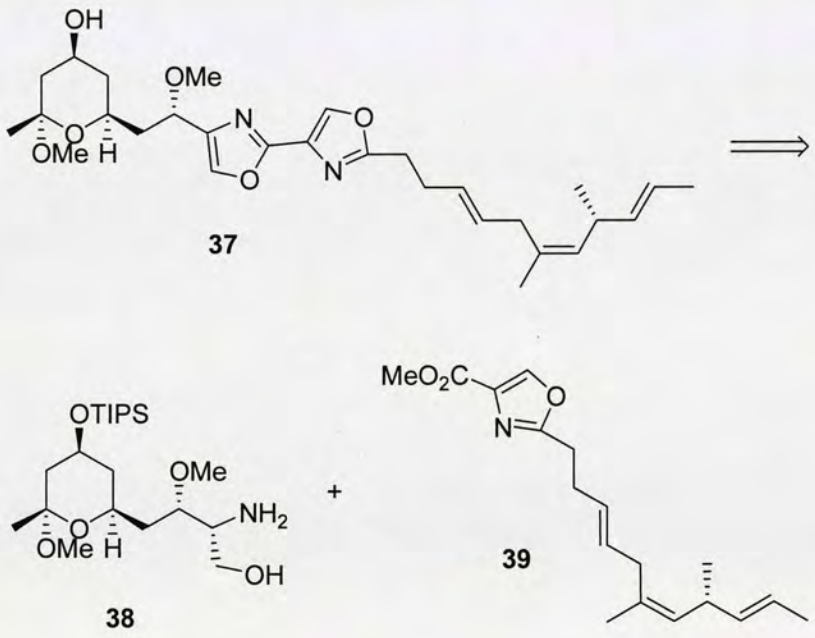
Figure 2. Structure of texaline.[40]

The number of oxazole moieties in natural products can vary widely. Single oxazole containing structures such as texaline (**36**) (Figure 2) are known, as well as bisoxazoles, such as hennoxazoles, in which the oxazoles are connected directly to each other. Texaline, shown above, is a rare example of a 2,5-disubstituted oxazole.[40]

As mentioned above, one of the more prominent and potent bis-oxazole natural products in which large amounts of synthetic effort has been invested is (-)-hennoxazole A, an antiviral compound. Hennoxazoles are 2,4'-bis-oxazole-containing structures; they exhibit very good biological activity against the herpes simplex virus 1 (HSV-1) and in addition possess peripheral analgesic activity which is comparable to the one of indomethacin.[41]



37

38 + **39**

Scheme 11. (-)-Hennoxazole A and a key retrosynthetic step.[43]

Hennoxazole A was first isolated from *Ployfibrospongia sp.*, by Scheuer and co-workers and synthesised via a convergent approach by Yokokawa *et al.* in 2000, one of many reported total syntheses of this compound.[42,43] The key step in this total synthesis is a diastereoselective Mukaiyama aldol reaction. As previously described, the formation of the oxazole rings, which are linked together in a 2,4-fashion, was achieved using peptide chemistry (Scheme 11), followed by an oxidation of the cyclic oxazoline intermediate to the oxazole.

In addition, di-oxazole structures have been isolated in which the oxazoles are not directly coupled to each other, usually two carbons apart. Examples of this type of oxazole natural product are siphonazole (Figure 3) or the synthetically more challenging diazonamide A (Scheme 12). Recently Moody and Linder have disclosed their synthetic efforts towards the very interesting di-oxazole containing natural product, siphonazole.[44]

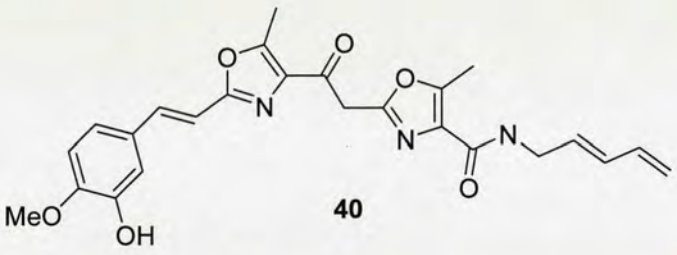


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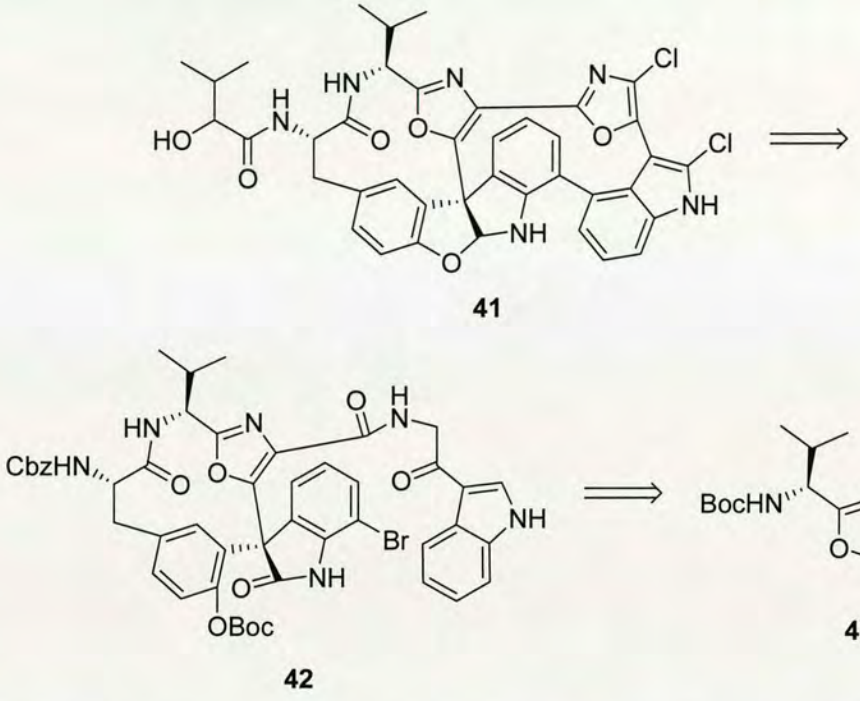
Figure 3. Structure of siphonazole.[44]

It is an interesting synthesis because of the way the oxazoles were generated. Unlike most other syntheses of oxazoles, Moody chose a rhodium carbene condensation reaction instead of the classical amino-acid approach. Both oxazole rings in this natural product were constructed using rhodium$^{(II)}$-carboxylates and diazocarbonyl reagents. The natural product was formed in an impressive ten steps using this non-traditional approach to oxazole synthesis.

A further prominent natural product, containing a pair of oxazoles, has been synthesised by several groups around the globe. Diazonamide A, an anticancer agent

and a bis-oxazole compound, isolated from a marine species found in the Philippines, has been synthesised twice (1st and 2nd approach) by Nicolaou and co-workers in an impressive fashion.[45,46]



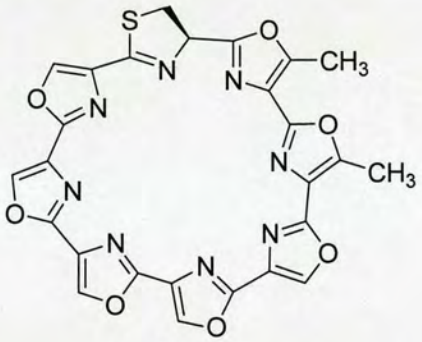
Scheme 12. The structure and proposed retrosynthesis of diazonamide A based on Nicolaou's work.[45,46]

The key step to form one of the two oxazole moieties in Nicolaou's second approach is a typical condensation / dehydration sequence as seen many times before and further discussed in this thesis. In this rather complex molecule however, the yield obtained was only 16 %. This yield can interestingly be directly compared to the yield of the formation of the first oxazole in diazonamide A (at the 3-position of indole) which was generated earlier in the synthesis in an impressive 88 % yield using similar conditions but on a very small, non-sterically hindered molecule at an earlier stage of the synthesis. This loss of yield is typical for these condensation reactions on larger, more sterically hindered molecules. It is also one of many reasons why a methodology, which does not involve the generation of these azoles in that fashion, would be very useful and of great value to the synthetic chemist. The harsh conditions usually employed in these dehydration / oxidation sequences could

very well be inappropriate should sensitive functional groups exist in the starting materials.

In addition to the above work from Nicolaou's group, other groups have published their synthetic efforts towards the synthesis of diazonamide A in the peer-review literature. Harran's as well as Magnus' group have both communicated their approaches towards this exciting structure.[47,48] Harran's synthetic efforts produced an alternative structure for the natural product, revising the original structure proposed via X-ray analysis.

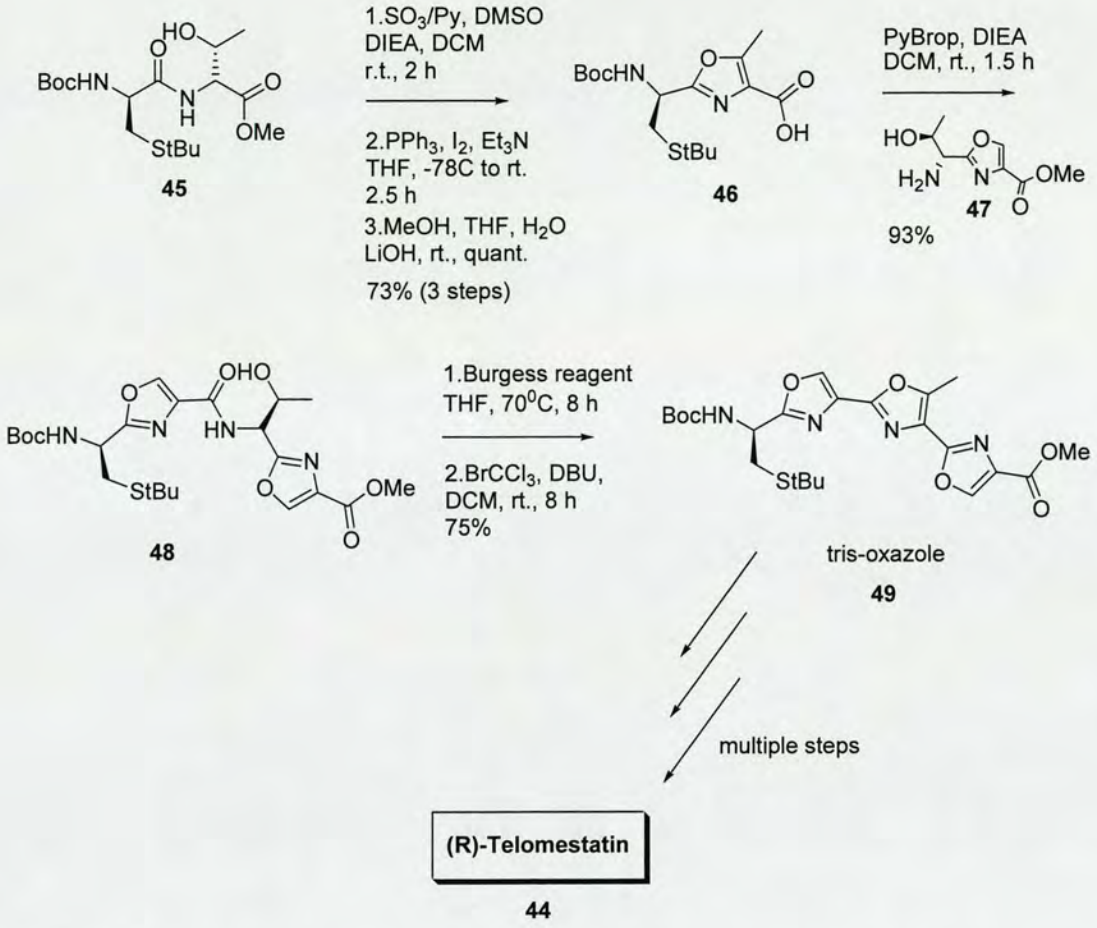
Oxazole-containing structures come in all shapes and forms, some of them, such as telomestatin (Figure 4), presenting up to seven linked oxazoles in a cyclic form. Telomestatin, a marine natural product isolated from *Streptomyces anulatus* is known to act as a telomerase inhibitor.[49]



44

Figure 4. Structure of telomestatin, a potent telomerase inhibitor.[49,50]

Telomestatin was first synthesised by Takayuki *et al.* in 2006 via a set of condensation reactions mimicking its biosynthetic pathway.[50] It should be noted that it's total synthesis had been reported prior to this 2006 publication but only in a patent by Taiho Pharmaceutical Co. Ltd. in 2002.[51]



Scheme 13. Synthesis of key-fragment in the total synthesis of telomestatin.[50]

Doi`s total synthesis of (R)-telomestatin commences with the oxidation of the secondary alcohol of the dipeptide **45**, followed by a cyclodehydration with PPh_3-I_2 in the presence of Et_3N. This sequence provided **46** in a respectable yield of 73 %. Hydrolysis of the ester to the acid, using LiOH, followed by coupling of the acid with the free amine **47** afforded bis-oxazole amide **48**. Another cyclodehydration, this time using Burgess` reagent, followed by $BrCCl_3$-DBU treatment of **48** gave Cys-containing tris-oxazole **49** in 75% yield.

The bio-mimetic synthesis to obtain these poly-oxazoles is to this date the most applied method and generally used by synthetic chemists. Starting materials are amino acids and peptides and the reactions follow a very general condensation / oxidation pattern. Examples of this approach are many, and compounds such as (-)-

hennoxazole A, (R)-telomestatin as well as mechercharmycin A (Figure 33, *vide infra*) have been generated via this approach.[50,52]

Other poly-oxazole and mono-oxazole natural products exist and have been synthesised. A group of Streptogramin antibiotics are representatives of the mono 2,4-disubstituted oxazole core. Virginiamycin M2, griseoviridin and madumycin II are all 2,4-disubstituted oxazole containing molecules and syntheses of these structures have been reported (Figure 5). [53-55]

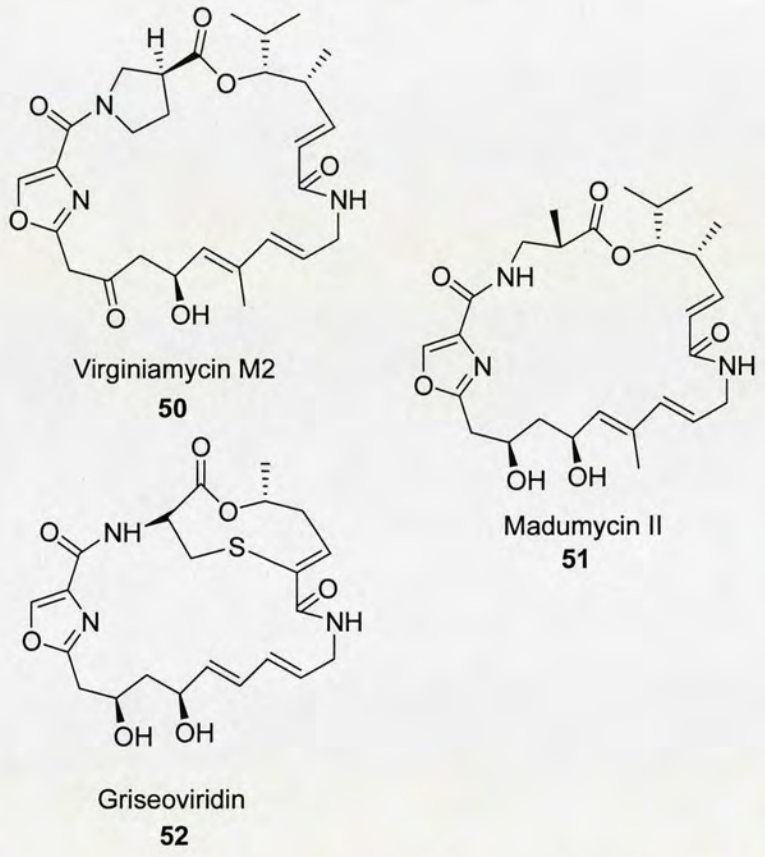


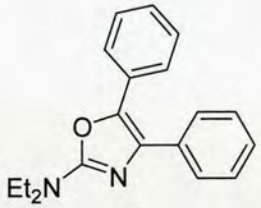
Figure 5. Structures of three group A Streptogramin antibiotics.[53-55]

Even though the vast majority of oxazole containing natural products are 2,4-disubstituted as in the examples seen above, there are a few cases of other substitution patterns, namely mono-substituted, 2,5-disubstituted as well as tri-substituted oxazoles such as the previously discussed diazonamide A.

Further, one can clearly see that most of the approaches to oxazole-formation in natural products, with a few interesting exceptions, have utilised classic cyclisation / oxidation or oxidation / condensation methods. Several other poly-oxazole containing natural products are discussed in more detail in the final chapter of this thesis.

1.1.4 Oxazoles in Medicinal Chemistry

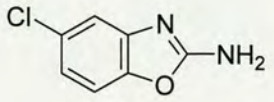
Oxazoles have also gained interest in industrial settings as more and more medicinal chemists are employing heteroaromatic compounds in the never ending quest for biologically active synthetic drugs and new chemical entities (NCE). Patent applications involving the oxazole core are not rare; reasons for this raised interest in azoles in general are the donor-acceptor (Lipinski's rule of five) abilities that oxazoles, imidazoles, thiazoles and others such as isoxazoles or pyrazoles, have to offer.[56,57] A few oxazole containing molecules have already managed to be marketed, the anti-inflammatory and analgesic 2-diethylamino-4,5-diphenyloxazole is one of them (Figure 6).[58]



53

Figure 6. 2-Diethylamino-4,5-diphenyloxazole, an anti-inflammatory drug.[58]

A further synthetic oxazole that has managed to appear on the market is zoxazolamine (Figure 7), a sedative and muscle relaxant, mechanism of action of which is not understood. Though it is no longer used, as it exhibits hepatic cytotoxicity, it is now a model substrate frequently used in studies on (methylcholanthrene-inducible) hepatic cytochrome P-450 activity.[59] The studies using zoxazolamine simply determine possible changes in oxidative enzyme activity on a pharmacological basis.

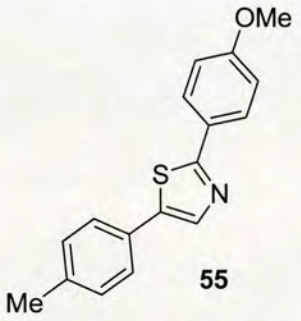


54

Figure 7. Zoxazoleamine, a synthetic muscle relaxant.[59]

From a medicinal chemistry standpoint, oxazoles have also gained popularity due to better and more effective methods to modify and / or generate them. Functional group transformations as well as the fairly new approach (as discussed in this thesis) of direct arylation have introduced a 'late stage diversification' approach compared to the 'classic peptide-condensation methodology' where the substituents around the azole ring have to be put in place early in the synthesis.

Most of the aryl-substituted oxazoles (or thiazole analogues) are also known to be highly fluorescent and are commonly used as scintillators and optical brighteners in industry.[49] Mori *et al.* have described the photoluminescence of such compounds in detail.[60] Their research shows the synthesis of 2,5-di-arylated thiazoles as well as di-substituted thiophenes via direct arylation and the potential electron-transporting characteristics of these compounds, which possibly makes them a useful component in LED devices.



55

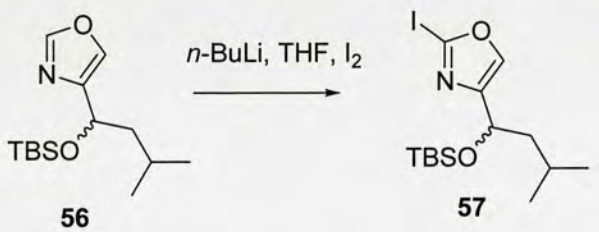
Figure 8. Highly fluorescent 2,5-disubstituted thiazole.

Mori *et al.* comment that the manipulation of the substituents on the aryl groups highly influences the light emitting characteristics of these compounds, a feature which we have also observed during the course of this research.[60]

1.1.5 Lithiation of Oxazole

Research into the lithiation of oxazole itself could form enough material for a complete thesis. It has been the centre of attention for several research groups over the years. It has been shown that upon treatment of oxazoles and benzoxazoles with strong bases, such as *n*-butyl-lithium or LHMDS, ring-opening of the oxazole at the two-position occurs.[61]

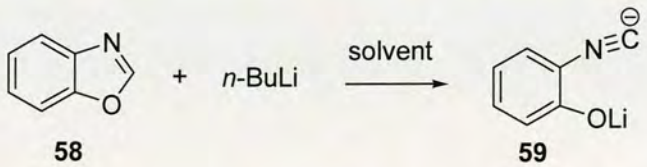
It has been demonstrated by Barrett and Kohrt that oxazole can be deprotonated in the 2-position using *n*-BuLi at low temperatures.[62] The oxazol-2-yllithium could then be quenched with iodine to give the product in an excellent 90 % yield. The reaction is invaluable as it provides easy access to important oxazoles for the use in transition metal catalysed cross coupling reactions as well as many other reactions depending on the electrophile used to quench the reactive species which is formed *in situ* via lithiation at low temperatures under inert gas atmosphere (Scheme 14).



56 **57**

Scheme 14. The halogenation of oxazole in the 2-position.[62]

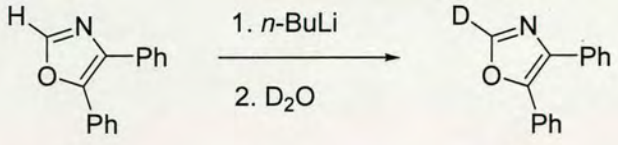
NMR studies on this phenomenon have been published and suggest an isonitrile functional group as well as the lithium salt of the phenoxide. Oxazole is the only one of the three 1,3-azoles (imidazole, thiazole and oxazole) that has been shown to exhibit such behaviour under basic conditions.[61]



58 **59**

Scheme 15. Ring opening of benzoxazole under strongly basic conditions.[61]

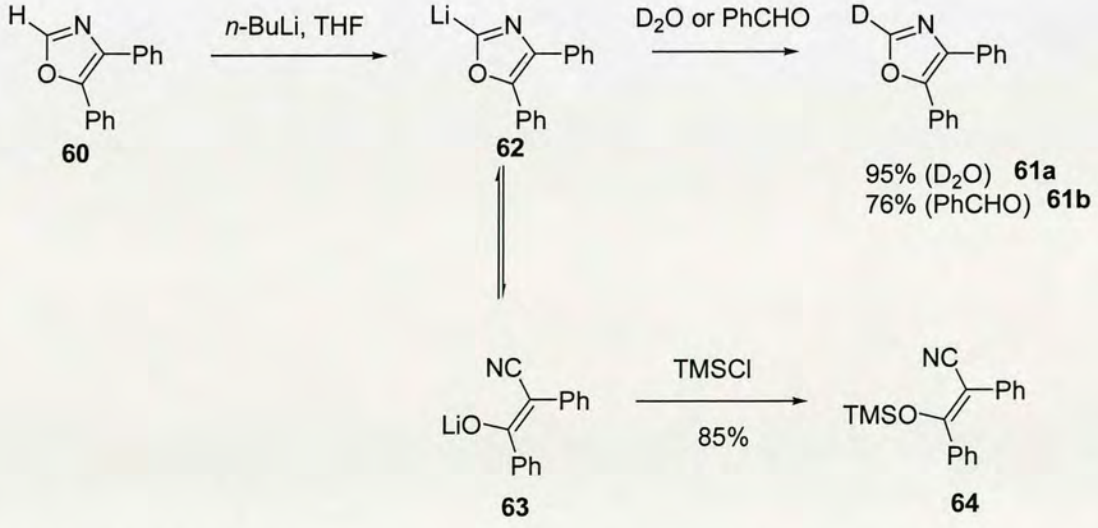
The first publication in this field of oxazole lithiation is a 1968 paper by Bowie *et al.* in which the group generated and observed the 2-lithium oxazole species using deuterated water by mass spectrometry.[63,64]



60 **61a**

Scheme 16. First lithiation of 2-unsubstituted oxazole followed by deuterium quench. [63,64]

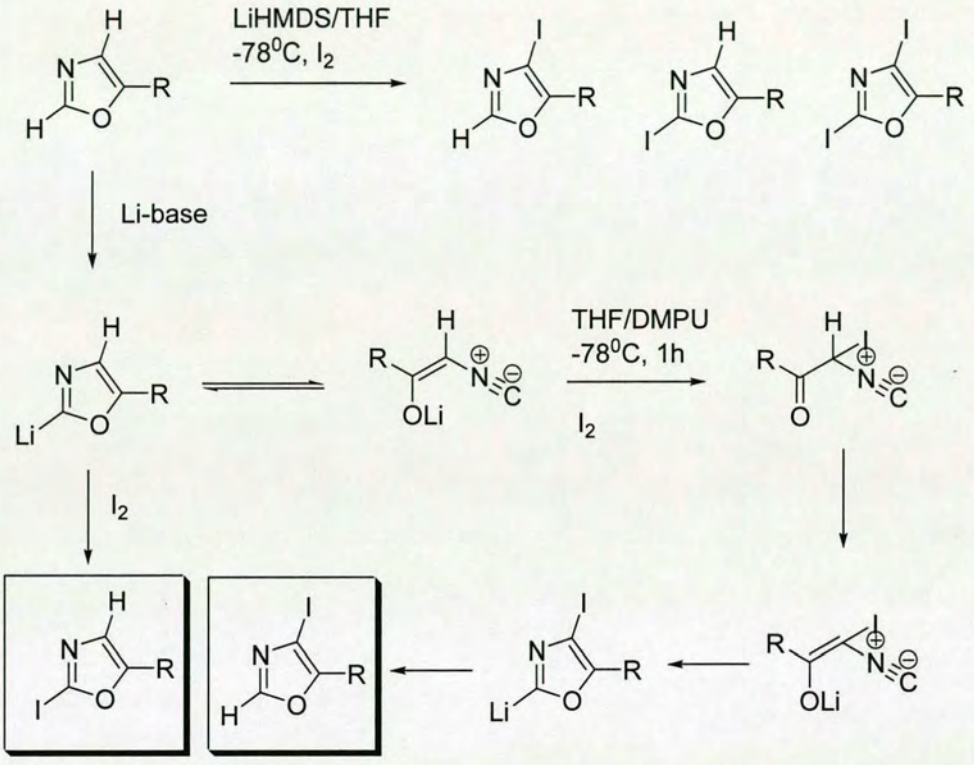
Further investigations into the lithiation of oxazole yielded very interesting results, showing an equilibrium between the cyclic and the acyclic form of oxazole, depending of the electrophile used. Schroeder and his colleagues showed that when using benzaldehyde or as above described deuterium oxide, the 2-substituted oxazole was generated in its cyclic form. However, when TMSCl was used as the electrophile, the ring-opened form was observed. [65]



60 **62** **63** **64**

Scheme 17. Schroeder's ring-opening and ring-closing tautomeric equilibrium of oxazole.[65]

Several articles and communications followed this early research describing the effects of different electrophiles and substituents on the oxazole, and the role they play in generating the cyclic or acyclic products. Vedejs and Luchetta recently published a method for the iodination of oxazoles at C4 using 2-lithiooxazoles.[61]



Scheme 18. Method for the lithiation of oxazoles at C4 via 2-lithiooxazoles.[61]

The authors purposely chose oxazoles, which when treated with a strong lithium bases would favour the acyclic valence bond tautomer, making the C4 position more readily available for halogenation than the C2 position. The authors further commented on their optimisation of the reaction conditions. It was noted that interestingly when DMPU was added as a co-solvent, selectivity and reproducibility increased and reactions gave up to a 97:3 ratio of 4-iodo-oxazole **66**.

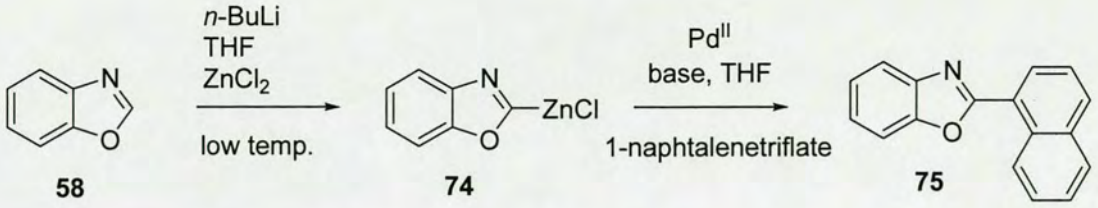
1.2 Palladium Catalysis on Oxazoles

1.2.1 Traditional Pd-catalysed Cross Couplings on Oxazoles

Before reviewing the catalytic approaches to C-C bond formation involving oxazoles, we would like to point out that, as to be expected, early stage research involved equimolar amounts of 'catalysts' and classical reactions such as electrophilic substitutions or simple redox chemistry.[66,67] These methods are not presented in detail here as this introduction is aimed to give an overview of contemporary palladium catalysis on oxazoles. Early oxazole reactions however have been collected and reviewed in detail and can be found in Palmer's oxazole book.[2]

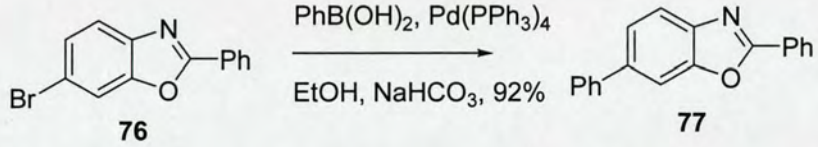
To this date there has been a limited amount of research directed towards palladium catalysed cross coupling reactions on oxazoles. In general there are five traditional approaches towards transition metal catalysed carbon-carbon bond formation reactions on oxazoles, namely the Negishi coupling (zinc), the Suzuki reaction (boronic acids / esters), the Stille (tin), the Sonogashira (alkynes / copper) as well as the well known Heck reaction (alkenes). In addition to these reactions, C-N bond formation has been accomplished and recently the functionalisation of oxazoles has also been achieved using direct arylation methodologies, which will be the main focus of this thesis.

The Negishi coupling uses oxazole (or benzoxazole), which is treated with a strong base to deprotonate the 2-position and then subsequent addition of $ZnCl_2$ generates the 2-chlorozincbenzoxazole species which is known to favor the cyclic form of oxazole.[68] The zincate then reacts with triflates (or halogens) such as 1-naphthalene triflate and a Pd^0-source at reflux to afford the cross-coupled products. This methodology proves very effective and many examples of 2-substituted oxazoles have been prepared via this approach (Scheme 19). From the three possible positions for the formation of organozinc reagent (on oxazole parent heterocycle), only the 2-oxazolylzinc species has been successfully prepared and subsequently cross-coupled with aryliodides and triflates.[68,69]



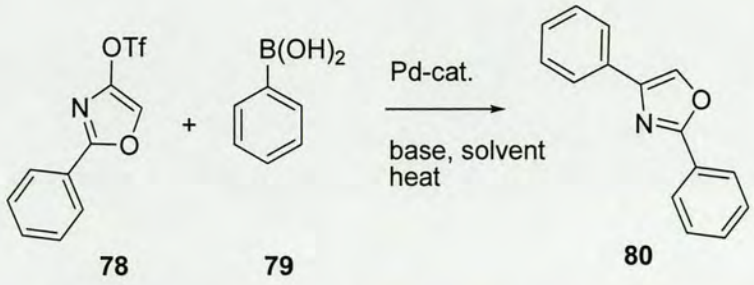
Scheme 19. Negishi reaction of benzoxazole using $ZnCl_2$ at low temperatures.[69]

A more detailed example of the mentioned Suzuki reaction on oxazoles is the transformation of **76** with phenylboronic acid to give **77** in 92 % yield. Most attempts (also attempted in the Greaney group) of generating 2-oxazolylboronic acids and esters have failed due to the probable equilibrium between the cyclic and acyclic valence tautomers of the lithiooxazoles which make this position highly reactive and *in situ* formed products prone to decomposition and protodeborenation.[1]



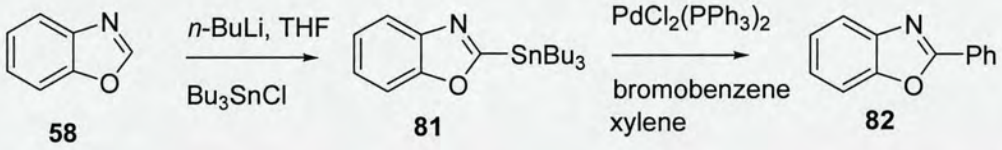
Scheme 20. Example of a Suzuki coupling involving a substituted benzoxazole.[70]

Note that the cross coupling was achieved on a bromo-benzene analogue, not actually on the oxazole core. More relevant when discussing oxazole C-C bond formations is the Suzuki reaction published by the Greaney group in 2006. Using a previously synthesised 2-substituted oxazole pseudohalide, a range of aryl boronic acids were coupled in excellent yields.[71]



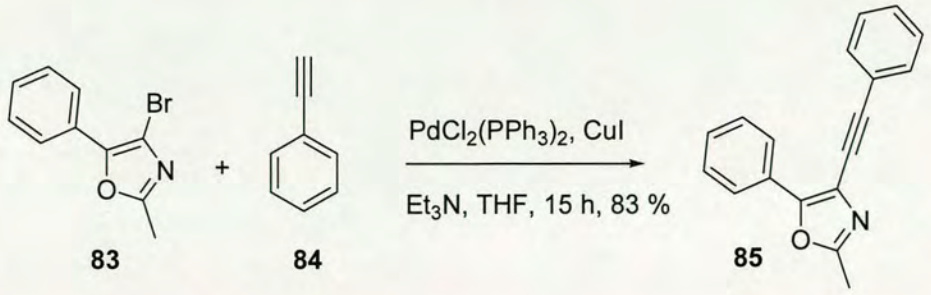
Scheme 21. Carbon-carbon bond formation using microwave conditions in the Suzuki reaction of oxazoles.[71]

Another very prominent reaction of oxazoles is the mild and base free Stille reaction.[72] Similar to the Negishi reaction stannanes can be generated via the trapping of a previously generated ring-opened oxazol-2-yllithium species with tributyl tin chloride. These substrates can then be attached to a range of aryl halo-compounds (Scheme 22). However, toxicity of the stannane and the generation of toxic side products are always a concern when utilising the Stille reaction.



Scheme 22. The Stille reaction of benzoxazole to 2-phenylbenzoxazole.[72]

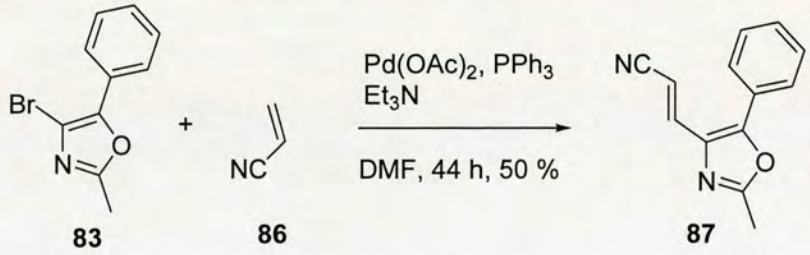
One of very few examples of a Sonogashira reaction of oxazoles is Yamanaka's Pd-catalysed reaction of terminal alkynes with a substituted 4-bromo-oxazole (**83**) at elevated temperatures. Several internal alkynes were synthesised using this methodology.[73]



83 **84** **85**

Scheme 23. Yamanaka's *et al.* approach to internal acetylenes on oxazoles.[73]

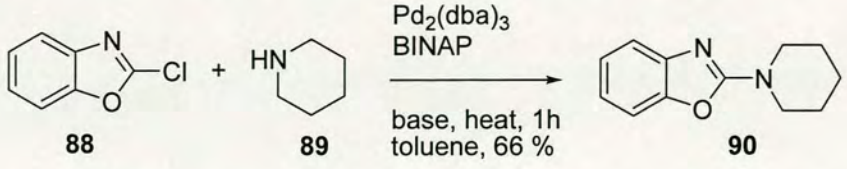
Using the same starting material (**83**) as for the Sonogashira reaction, Yamanaka also coupled electron-deficient terminal alkenes in Heck reactions with moderate yields.[73]



83 **86** **87**

Scheme 24. Heck reaction of oxazoles performed in the Yamanaka group.[73]

To complete the introduction of traditional C-C bond forming reactions on oxazoles we also have to look at a C-N bond formation reaction, which has been shown to work using oxazoles. This example, one of very few, shows that it is possible to couple secondary amines (**89**) to halo-oxazoles (in this case 2-chloro benzoxazole (**88**)) using palladium catalysis as well as a BINAP ligand (Scheme 25).[74]



88 **89** **90**

Scheme 25. C-N bond formation reaction on oxazoles via Buchwald's catalytic amination.[74]

As one can clearly see there is still a very large area of untouched chemistry in this field as a substantial amount of the chemistry developed until today focuses on the 2-position of oxazole. Most of the examples published used oxazoles with the 4- and 5-positions blocked, benzoxazole being the prime example. It would therefore be of great interest to use the different reactivities of the three carbons in oxazole to investigate regioselective modifications of this heterocycle. Recent synthetic investigations of groups around the world have targeted the development of new cross coupling methods such as the C-H functionalisation of azoles, including the oxazole moiety.

Cross coupling reactions of azoles with two or more heteroatoms have recently been reviewed in detail by Stanetty and co-workers.[75]

1.2.2 Direct Arylation Cross Couplings

Direct and selective transformation of C-H bonds to new bonds such as C-C, C-O or C-N has always been a goal for organic chemists.[76] Transformations involving C-H bonds have great potential, as C-H bonds are found in almost all organic molecules. Steroids, terpenes, alkaloids, carbohydrates as well as many other structures such as azoles provide many carbon-hydrogen bonds for putative functionalisation via transition-metal catalysed direct arylation. It should be noted at this point that in the literature the terms C-H bond activation, C-H bond functionalisation, cross-dehalogenative coupling as well as direct arylation have been used to describe the transformation discussed in scheme 26.

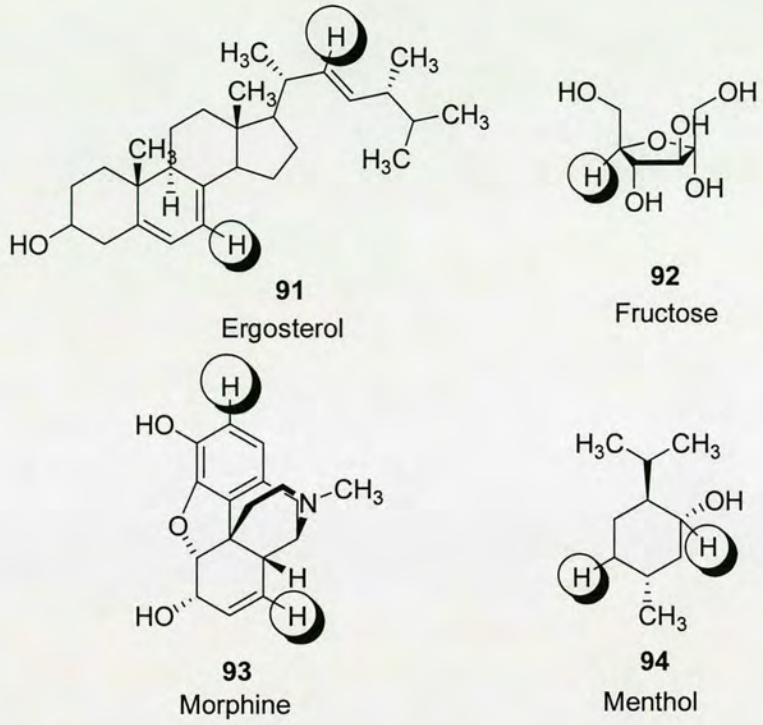
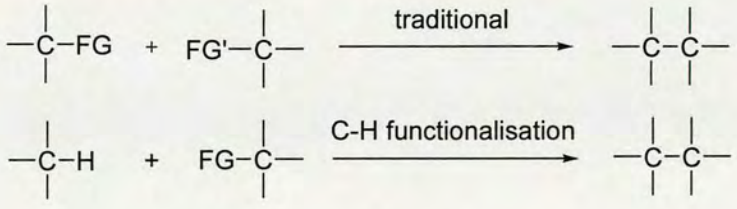


Figure 9. C-H bonds highlighted in several general groups of molecules.

Traditional cross-coupling reactions via functional group transformations generally require an equimolar amount of halide on one of the reactants as well as an equimolar amount of metal, such as tin, zinc, copper or magnesium on the other. The utilisation of a direct arylation approach eliminates the need for the metal component as the C-H bond replaces the metal. This therefore reduces the waste generated and eliminates the use of toxic metals such as tin. In addition, the atom economy of the reaction is increased immensely as the metal, generally of high molecular weight, is replaced by the smallest possible atom, hydrogen.[77]



Scheme 26. Comparison between traditional and direct arylation sp^2 C-C bond forming approach.

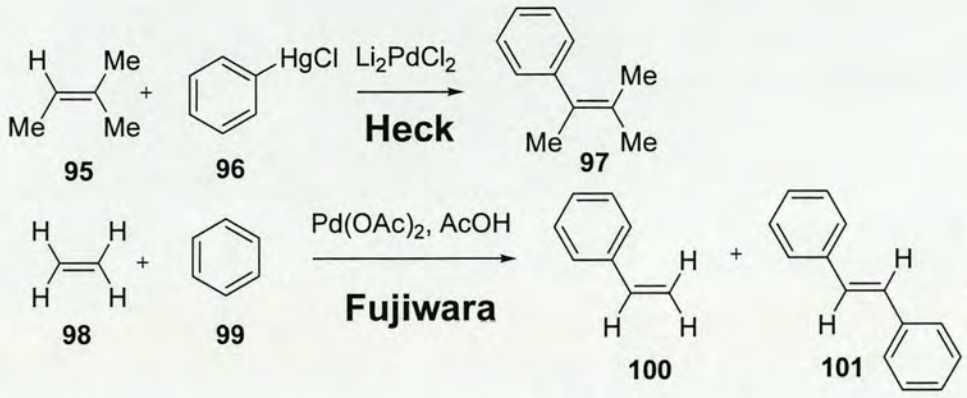
Currently the main challenge for the direct arylation of such complex and challenging molecules remains to be the regioselectivity. Many examples of direct arylations have been reported in the literature to this date, some of the most exciting ones are highlighted below. Indoles, pyridines, thiophenes, pyrroles, furans, isooxazoles, indolidines, imidazoles, oxazoles and other heterocycles all have been shown to be arylated on a C-H bond.[78-84] Further the N, S and O-arylation has recently been shown to work via iron-catalysed transformations.[85,86]

The field of direct arylation has been reviewed extensively in the last decade. A superbly detailed review by Lautens *et al.* highlights the advances in the area and discusses future directions.[87] A further recent review by Miura and Satoh also discusses the catalytic direct arylation of heteroaromatic compounds.[88] Additional reviews have been produced by Labinger and Bercaw, Fagnou, Godula and Sames, Sanford and Dick, as well as McGlacken and Bateman.[89-93] Upon reading these reviews, the reader can clearly see that the direct arylation of azoles, oxazole and pyrazole in particular was a rather untouched field when research into this project was commenced in 2006.

1.2.2.1 General Direct Arylations

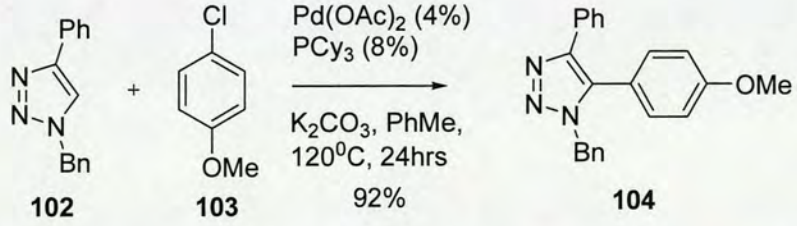
The examples in the section below have been selected to represent the broad and diverse applicability of current direct arylation methodologies.

Before investigating the Pd-catalysed direct arylation of oxazoles the Pd-catalysed direct arylation of other aromatic and heteroaromatic compounds is highlighted. In the literature, Fujiwara and co-workers are credited with the first true palladium promoted direct arylation reaction to form a C-C bond. The authors of this 1969 publication constructed C-C bonds from arenes and with it, started the field of direct functionalisation of aromatic arenes.[94]



Scheme 27. First ever direct arylation / C-H functionalisation (equimolar Pd) by Fujiwara *et al.*[94]

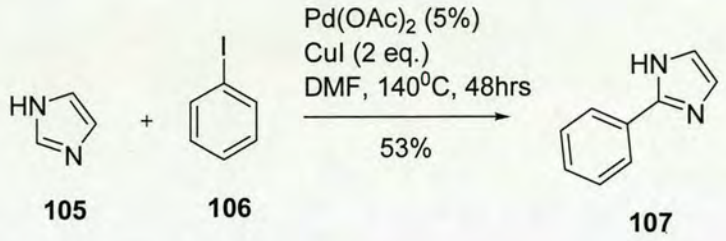
Several reports in the following few decades were published on the topic of palladium catalysed direct arylation and have recently been reviewed in detail by Shi, Yang and Li.[95] Much more recent than the Fujiwara report and not included in the review is Ackermann and his co-worker's report on the palladium catalysed direct arylation of 1,2,3-triazoles with aryl-chlorides using conventional heating.[96] In this 2008 report, *N*-alkyl and *N*-benzyl substituted 1,2,3-triazoles were reacted with cheap aryl-chlorides to afford fully substituted triazoles. High temperatures as well as a $Pd(OAc)_2$ / PCy_3 in combination with K_2CO_3 and toluene provided the products in good to excellent yields. Scheme 28 shows a representative example.



Scheme 28. Ackermann *et al.* described the direct arylation of 4-substituted 1,2,3-triazoles.[96]

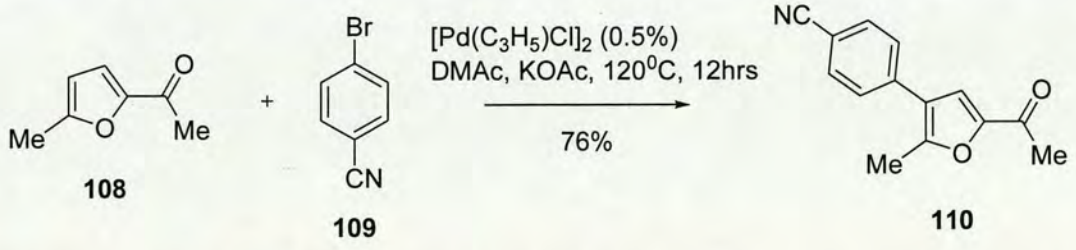
A publication from Bellina *et al.* was disclosed in 2006 providing insight into the direct arylation of NH-free imidazoles.[97] The parent heterocycle **105** was arylated in the 2-position using a catalytic amount of palladium in combination with two

equivalents of CuI. DMF as well as forcing 140°C were used to generate a series of 2-substituted imidazoles. It should be noted that when omitting the CuI, the selectivity decreases and 5-arylation can be observed.[97] This is typical for thiazoles and imidazoles.[75]



Scheme 29. Pd and Cu co-catalysed direct arylation of NH-free imidazoles.[97]

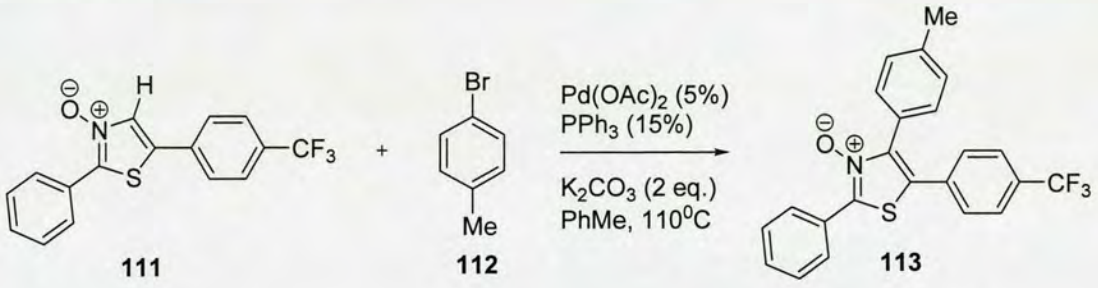
Doucet and Gottumukkala in 2008 published a palladium catalysed direct C4 arylation of 2,5-disubstituted furans. The work describes the mono- and di-arylation of 2,5-disubstituted furans with arylbromides under elevated temperatures. Blocking of the 2- and 5-position of the furans is necessary to circumvent the direct arylation on those positions. Diarylation has also been observed by the authors and was mentioned as a major problem for this transformation. Use of 0.5% Pd-catalyst as well as arylbromides however make this reaction fairly attractive.[98]



Scheme 30. Doucet's palladium-catalysed direct arylation of 2,5-disubstituted furans.[98]

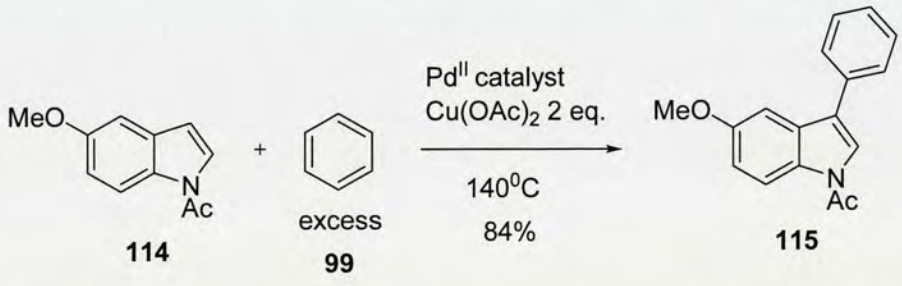
Also in 2008, Fagnou's research group communicated the direct arylation of azole N-oxides. Interestingly the N-oxide group dramatically increases the reactivity of all positions of thiazoles towards direct arylations. It also changes the weak azole bias of C5 > C2 to a very consistent C2 > C5 > C4. This increased reactivity and

regioselectivity allows for the stepwise functionalisation and synthesis of a tri-aryl-substituted thiazole N-oxide. The N-oxide functionality can later be removed by deoxygenation.[99]



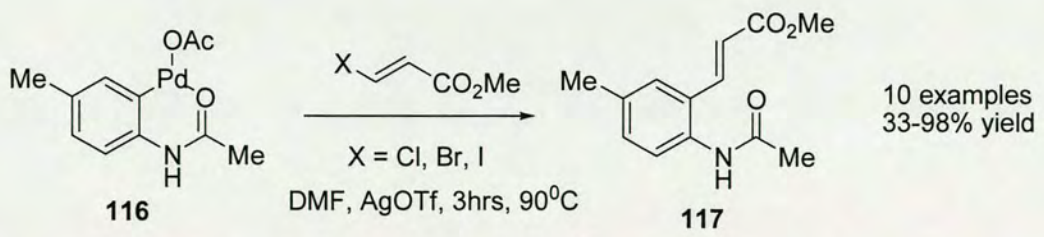
Scheme 31. Fagnou's N-oxide promoted direct arylation of thiazole.[99]

Fagnou's group as well as others have also invested a vast amount of research into the regioselective direct functionalisation of the indole heterocycle, this work has recently been reviewed.[100] The clear highlight of the indole direct arylation to date is the oxidative coupling of *N*-acetyl indole (**114**) with benzene (**99**), as reported by Fagnou in 2007. The publication describes the coupling of two C-H bonds with each other under palladium catalysis with an equimolar amount of oxidant. Scheme 32 shows this exciting transformation in more detail.[101]



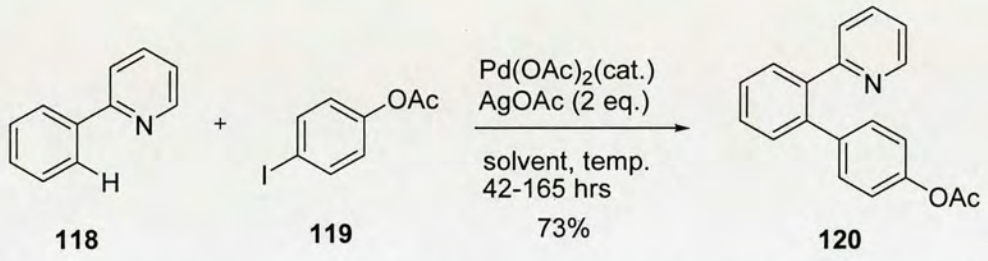
Scheme 32. Fagnou's direct arylation of an indole-analogue using benzene.[101]

Daugulis and Zaitsev have reported the catalytic coupling of haloolefins with anilides. In this highly challenging and interesting transformation the carbonyl group acts as a directing group for the electrophilic palladium which inserts into the C-H bond.[102]



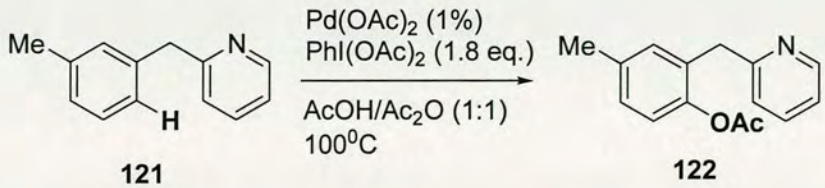
Scheme 33. Daugulis' C-H activation of anilides with haloolefins.[102]

Daugulis also described the palladium catalysed *ortho*-arylation of heteroaromatic biphenyl motives as shown in scheme 34.[103]



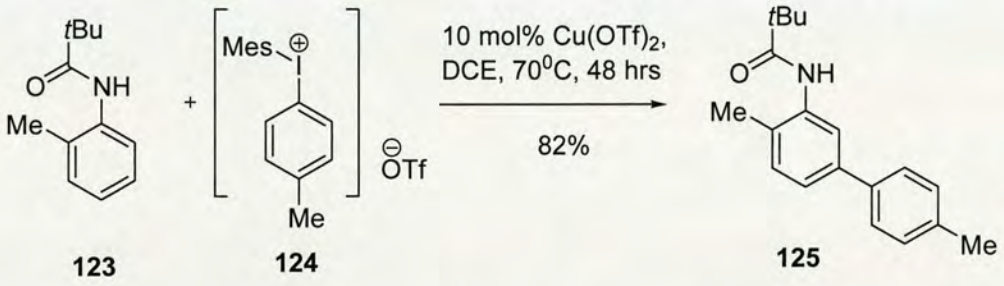
Scheme 34. Daugulis and co-workers *ortho*-functionalisation using palladium.[103]

A further well known example showing the directing group abilities of pyridines, isooxazolines, pyrazines and pyrazoles is Sanford's Pd-catalysed ligand directed arene acetoylation. Several series of benzyl-substituted compounds including benzyl pyridine derivatives were used to generate *ortho*-functionalised aromatic rings as described below.[104]



Scheme 35. Palladium catalysed ligand directed arene acetoylation.[104]

Lastly, the highlight of the year 2009 in terms of direct arylation research is presented. Although this is a non-palladium catalysed procedure, I still believe that this exciting transformation should be highlighted in this section as it shows the strength and impact simple methodology projects can have on the general chemistry community. Gaunt and Phipps reported a *meta*-selective direct arylation using Cu-catalysis. This is a remarkable discovery of reactivity and undoubtedly complements the Pd-catalysed direct arylation methods for the *ortho*-arylation. *Meta*-C-H-bond cupration via dearomatizing 'oxy-cupration' has been hypothesised to be the key mechanistic transformation.[105]



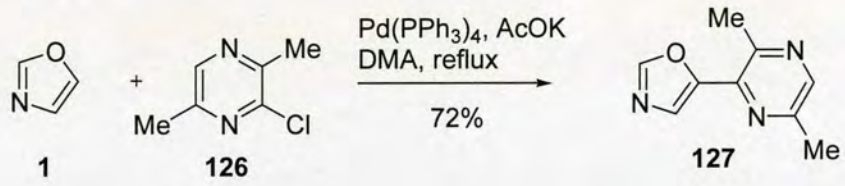
123 **124** **125**

Scheme 36. Phipps' and Gaunt's Cu-catalysed *meta*-arylation.[105]

While a base is normally needed for direct arylation reactions, in many cases the precise role of the base is unclear. Some new evidence, however, suggests that in a few systems the base could be intimately involved in the formation of the diarylpalladium$^{(II)}$ species (and not just as a bystander whose role is to regenerate the active catalyst)[106a-c] Generally, inorganic bases such as K_2CO_3, Cs_2CO_3, KOAc, *t*-BuOK and CsOPiv are used and have shown to be effective in multiple cases due to increased solubility in organic solvents. Commonly used solvents are DMSO, NMP, CH_3CN, DMF and DMA, nonpolar solvents such as xylene and toluene have also been shown to promote these kinds of transformations. Finally, temperatures of 100 °C and above are generally used and typical reaction times range from several hours to days.[106a-c]

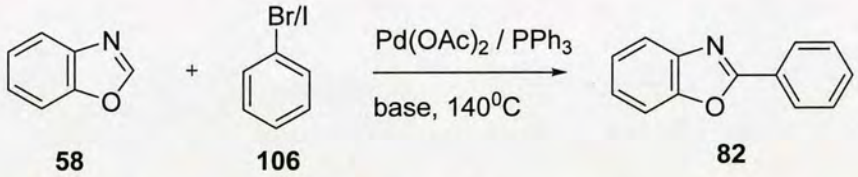
1.2.2.2 Direct Arylation of Oxazoles

The first reported direct arylation of an oxazole analogue is Ohta's reaction of oxazole (**1**) with a chloropyrazine (**126**), which selectively couples to the 5-position of oxazole. The conditions described in this 1992 publication are a potassium base as well as $Pd(PPh_3)_4$ (5 %) as the catalyst of choice.[107]

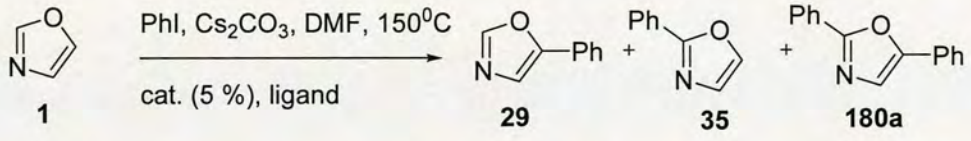


Scheme 37. Ohta's direct arylation of oxazole.[107]

Several years after this communication, Miura *et al.* provided an arylation of benzoxazole with aryl iodides and bromides.[108] Useful bases for this transformation were reported to be K_2CO_3 as well as Cs_2CO_3. The coupling was achieved in DMF as a solvent and $Pd(OAc)_2$ (5 %) with PPh_3 as catalyst and ligand, respectively. Yields for these early transformations were reported to be as high as 95 % when CuI was used as a co-catalyst.[108]



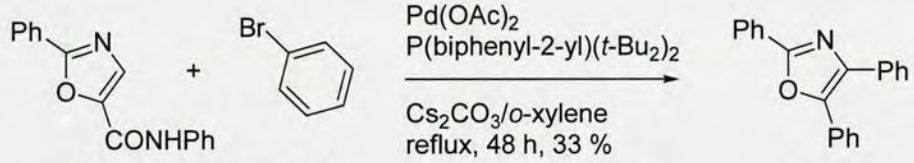
Scheme 38. Miura's report of a direct arylation of benzoxazole.[108]



Scheme 39. Early attempts by Miura to achieve regioselectivity gave mixtures of three different products.[109]

Following these discoveries, the field of direct arylation on oxazoles turned quiet for a few years, until Sames' report of an arylation of the parent oxazole heterocycle using catalytic amounts of copper. This report was however retracted on June 15th, 2006.

Following Miura's 1998 discoveries, only three reports until 2006 were communicated in the peer-reviewed literature. In 2003, a report again by Miura on the arylation of thiazoles appeared in the literature. This report included, next to several thiazole arylations, a palladium catalysed direct arylation on a di-substituted oxazole.[110]

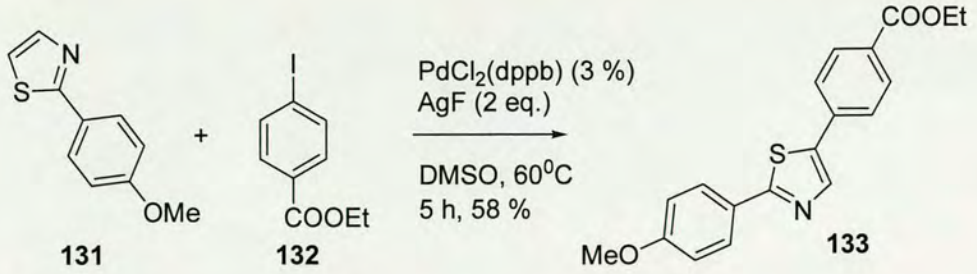


128 **129** **130**

Scheme 40. Generation of a tri-phenyl oxazole via direct arylation.[110]

It is noteworthy that the starting material does not contain two phenyl groups, but rather has them introduced in the direct arylation step. It seems that the amide acts as a directing group to coordinate palladium and therefore brings the aryl-bromide (post-oxidative addition onto the Pd) in proximity of the 4-position, which is known to be notoriously unreactive towards any direct arylation conditions. Miura does not further comment on the loss of the amide functionality on the 5-position or any directing effect of the NH-functionality.

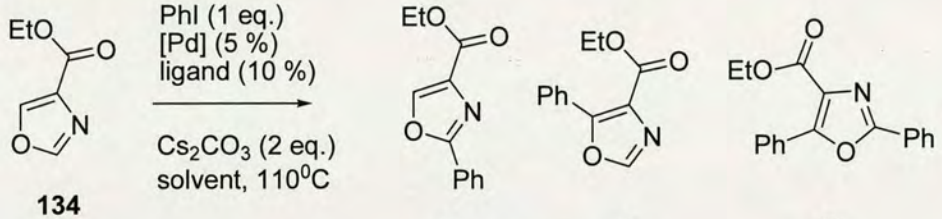
A year later, Mori and colleagues reported a direct arylation of thiazoles in DMSO, and Hoarau and co-workers presented a study on the regioselectivity of direct arylations on ethyl-4-oxazolecarboxylate (**134**) investigating a number of ligands and palladium sources.[111]



131 132 133

Scheme 41. Formation of 2,5-diarylated thiazole (**133**) in DMSO using silver salts for the first time.[111]

Table 2. Conditions provided by Hoarau and co-workers.[112]



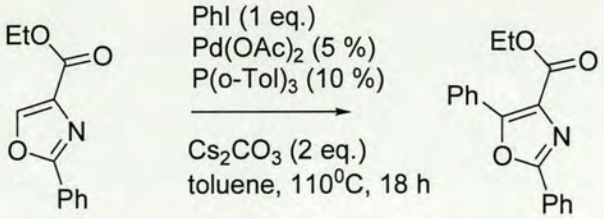
134

A 135 B 136 C 137

Entry	[Pd]	Ligand	Solvent	A (%)	B (%)	C (%)
i)	$Pd(OAc)_2$	PPh_3	Dioxane	30	12	17
ii)	$Pd(OAc)_2$	PPh_3	DMF	40	0	0
iii)	$Pd(OAc)_2$		Dioxane	46	0	0
iv)	$Pd_2(dba)_3$		NMP	41	0	0
v)	Pd/C		NMP	0	0	0
vi)	$Pd(PPh_3)_4$		Toluene	20	2	6

We are aware that there is no example of an oxazole arylation in Mori's 2004 publication, but chose to include this report in the introduction of this thesis due to the importance of Mori's example to the research of this thesis.

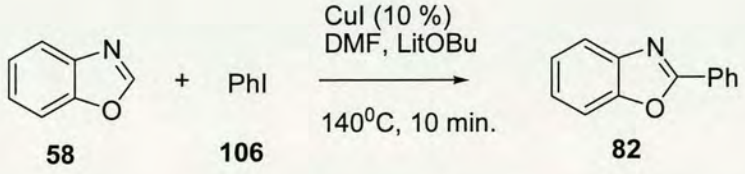
In Hoarau's report we also find the first discussion on the mechanistic nature of this oxazole arylation. This topic shall be further discussed later in this chapter.



135 **137**

Scheme 42. Hoarau's optimised conditions (96 % yield) for the arylation of oxazole on the 5- position.[112]

The only other publication of oxazole arylation methodology prior to the submission of our results was a landmark paper by Daugulis and co-workers.[113] In this report, Daugulis *et al.* reported the catalytic use of CuI in DMF at 140 °C using a lithium base such as Li^{t}OBu to arylate benzoxazole (**58**) on the 2-position in less than 30 minutes. Many examples (Ar-I and Ar-Br) are presented and the commercial availability of the starting materials and reagents make this a very useful method. Not only oxazoles have been shown to be arylated with these conditions, thiazoles, triazoles, purines as well as N-oxide-pyridines also work in good to excellent yields. Drawbacks of this method are the high reaction temperatures as well as the use of DMF as the solvent.

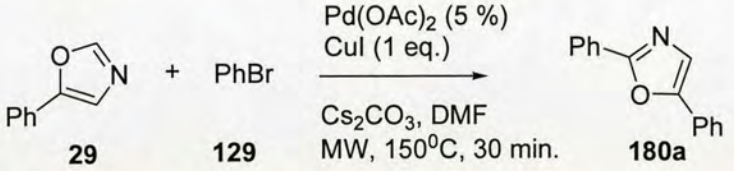


58 **106** **82**

Scheme 43. Daugulis' copper catalysed direct arylations on oxazoles.[113]

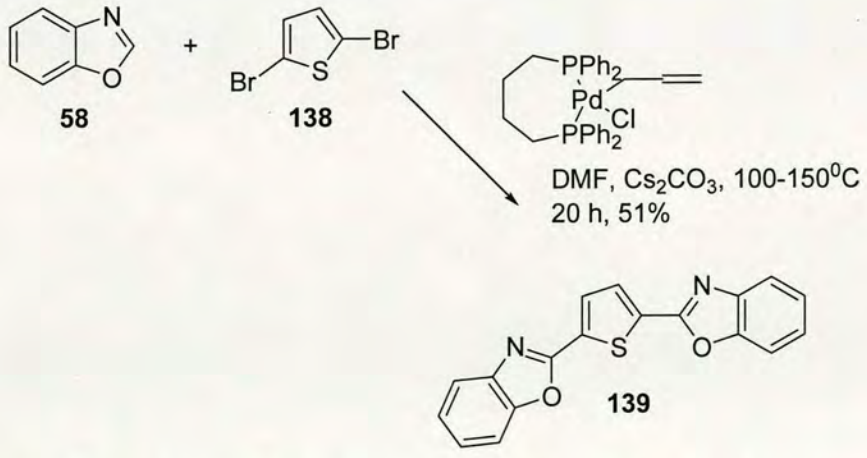
The following examples of oxazole direct arylations have appeared in the literature after our first manuscript was accepted and published. To complete and obtain a full review of oxazole arylations to the date of submission of this thesis, the following articles must nevertheless be discussed in detail.

A microwave-assisted method for the arylation of oxazoles has been reported in 2008 and uses a Pd / Cu co-catalyst system. Reactions are performed at high temperatures in a sealed tube. The authors reported the use of 5-phenyl-oxazole (**29**) with a variety of aryl-bromides. Optimised conditions include the use of Cs_2CO_3, $Pd(OAc)_2$, CuI (1 eq.) in DMF. Several small 2,5-diarylated natural products have been synthesised using this method and are reported with moderate yields.[114]



Scheme 44. Microwave assisted synthesis of 2,5-diarylated oxazoles.[114]

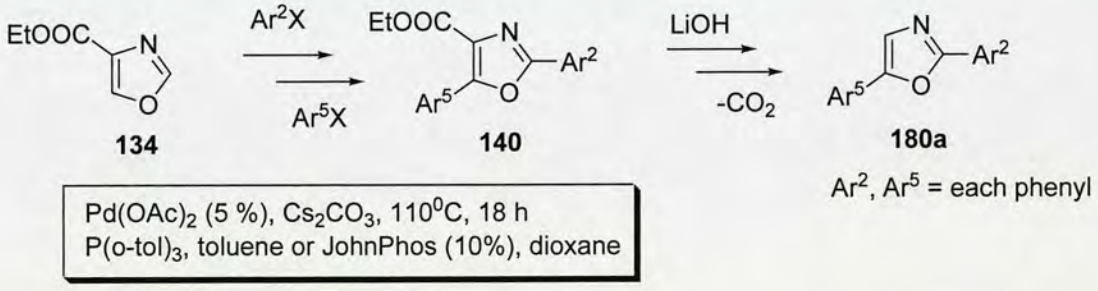
Another 2008 report on the direct arylation of benzoxazole (regioselectivity obviously not an issue when using benzoxazole) has been disclosed by Derridj *et al.*. The authors generated symmetrical molecules using their own catalyst, benzoxazole (**58**) and 2,5-dibromothiazole (**138**) at high temperatures. In addition the authors show that their developed methodology works for the arylation of benzoxazole with several electron poor and electron rich aryl-bromides.[115]



Scheme 45. Derridj *et al.* Pd-catalysed direct arylation of benzoxazole with di-bromo-thiophene.[115]

Following the discovery of the reactivity of the 2-position of oxazole towards direct arylation under the 'on water' conditions described in this thesis, Ferrer-Flegeau *et al.* explored the scope of this methodology first described in this thesis, in detail. The initial results of the 'on water' 2-arylation of oxazole are reported in this document and all the work that followed this discovery is discussed further in the following chapters.[116]

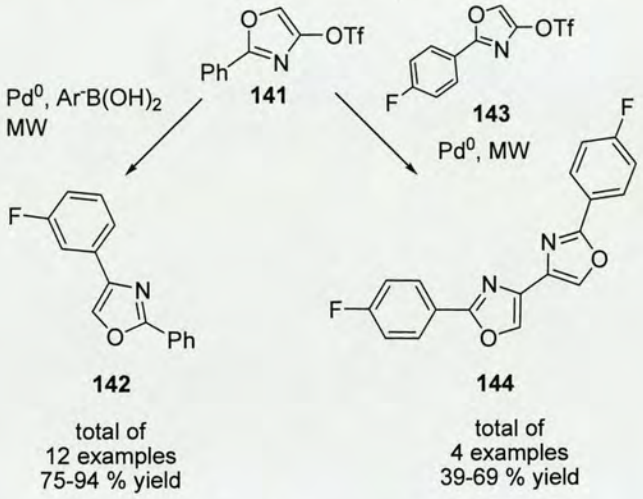
Lastly and most recently, Hoarau and colleagues have reported an interesting method to generate 2,5-diaryl-oxazoles.[117] Starting from ethyl-4-oxazolecarboxylate (**134**), the authors selectively arylate the 2-position followed by the 5-position with different conditions. Most interestingly is the use of aryl-chlorides as coupling partners, aryl-chlorides have so far not been used in a general way for the direct arylation of oxazoles. The authors of this communication provide high yields for aryl-iodides, aryl-bromides as well as aryl-chlorides. It seems that the ligands JohnPhos or IMes are the crucial components in these cross coupling reactions as yields drop to zero should any other ligands be used in these couplings. Further, the authors use a saponification / decarboxylation sequence to generate the vacant 4-position on the oxazole. Final compounds generated by this methodology are similar to the ones reported in this thesis.[117]



Scheme 46. Synthesis of 2,5-diarylated oxazoles via step-wise arylation of 4-substituted oxazole.[117]

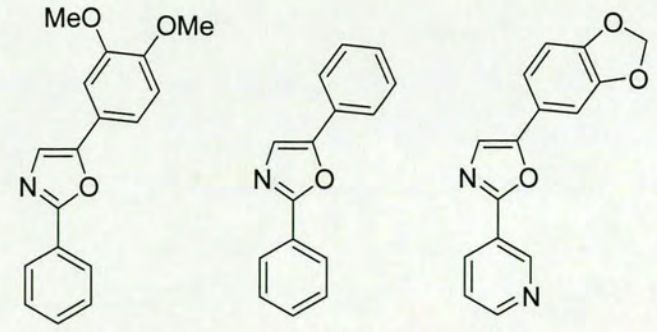
1.3 Aims of Project

Following recent advances in the Greaney group in the functionalisation of the 4-position of oxazoles via C-C bond formation using the broadly applicable Suzuki coupling and the general availability of arylation methods on the 2-position (see introduction), we set out to develop a methodology to regioselectively substitute the 5-position using a direct arylation approach and therefore provide easy access to useful compounds that have been modified at a late stage of the synthesis.[71]



Scheme 47. Ferrer-Flegeau and Greaney's oxazole Suzuki cross-coupling reaction using triflates.[71]

To develop and prove a methodology we needed an oxazole system where the 2-position is blocked, as it is the most acidic site and certainly reactive towards direct arylation conditions. We also wished that the 4- and 5-positions were still vacant. Target compounds to show potentially successful conditions were researched in the literature and gave several hits. Three of the targets proved very interesting, as they show either unusual physical properties or activities in biological assays (Figure 10).



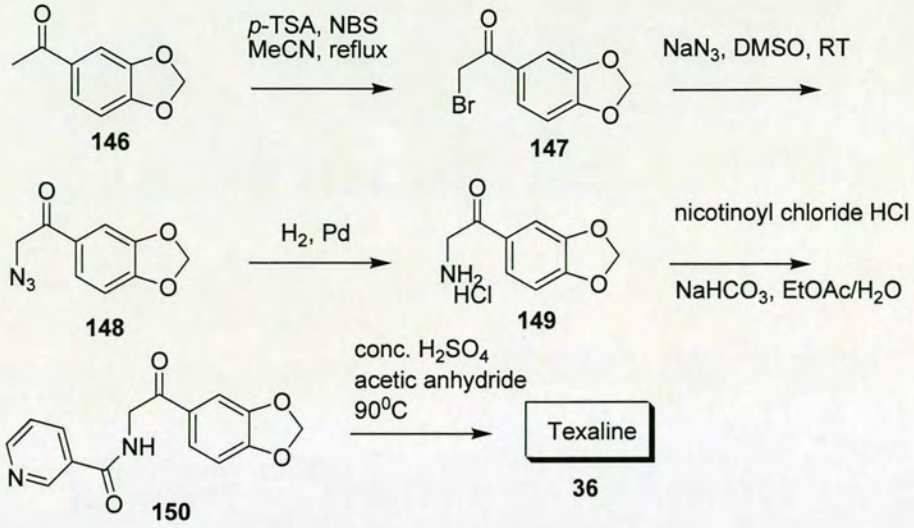
145 Balsoxin | **180a** 2,5-Diphenyl-oxazole | **36** Texaline

Figure 10. Structures of balsoxin, 2,5-diphenyl-oxazole and texaline.[118-120]

Two antimycobacterial natural products, balsoxin and texaline, next to several industrially useful scintillators such as 2,5-diphenyl-oxazole were identified.

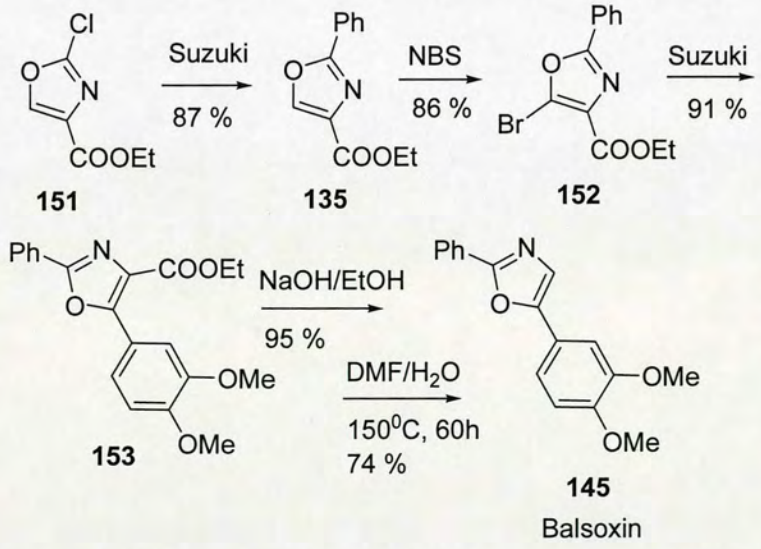
1.4 Previous Syntheses

Before synthesising the above mentioned compounds, previous syntheses of texaline and balsoxin were researched and carefully evaluated.[118,120] It turns out that both natural products had been synthesised only once before, both in five steps. Texaline via a lengthy and low yielding synthesis (overall yield 3.6 %) using a bromination, a reduction and a peptide coupling followed by an intramolecular condensation reaction to yield the product.[120]



Scheme 48. The only previously described synthesis of texaline.[120]

Balsoxin, in comparison, had been synthesised via C-C bond formations in fairly high yields. Two Suzuki-reactions, a bromination as well as a decarboxylation are presented and the natural product is synthesised in an respectable overall yield of 48 %.[118]



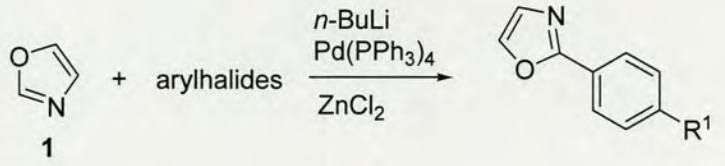
Scheme 49. Previous total-synthesis of balsoxin using a double-Suzuki approach.[118]

1.5 Results and Discussion

1.5.1 Preparation of Starting Materials

Given the already performed 4-arylation of oxazoles in the Greaney group, with the 2-position blocked, we set out to attempt to modify the 5-position selectively over the 4-position. If the mechanism of this particular reaction involves an electrophilic aromatic substitution, we should expect the 5-position of the oxazoles to be most reactive as it is the most electron rich site available. To be able to arylate the 5-position we first needed to synthesise several 2-substituted oxazoles. The selection of 2-substituted oxazoles as starting materials was based on the electronic effects the substituents would have on the oxazole. It was decided that an activated example (*p*-methoxy), a slightly less activated (*p*-methyl), a neutral (phenyl) and the inactivated example (3-iodo-pyridine) were to be used to show the broad applicability of this chemistry. Two general pathways to generate the 2-aryl-oxazoles have been attempted and were successfully used, each for its own reasons.

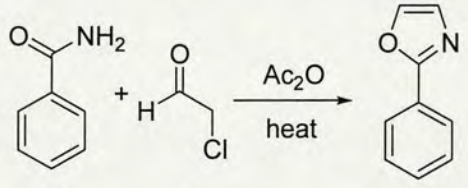
First of all the Negishi reaction between oxazole and several aryliodides was investigated and successfully used, generating the desired 2-arylated oxazole-products in excellent yields with a small amount of work-up. However, this reaction is costly as the parent oxazole core is expensive (34£ / g) when used in multi-gram quantities to generate large amounts of starting material for the direct arylation screening reactions.[121] Nevertheless three starting materials were synthesised in good yields using this method and have been fully characterised and matched the literature spectroscopic values. It is noteworthy that the addition of solid zinc chloride over the commercially available 1.6 M solution in THF is a better way to prepare these compounds as described by Reeder *et al.* The solid $ZnCl_2$ was added at once, under positive nitrogen pressure avoiding any moisture and air to enter the flask, via the addition at low temperatures.[121]



R^1 = CH_3 (75 %) **154**
= OCH_3 (86 %) **155**
= H (78 %) **35**

Scheme 50. Negishi reactions to generate 2-substituted oxazoles via C-C bond formation.[121]

The second approach and synthesis of 2-substituted oxazoles is the modified Robinson-Gabriel synthesis of oxazole using benzamides (Scheme 51). This reaction is best described as messy and sluggish as after a few hours of heating, not all the starting materials are consumed at this point, large amounts of polymer-type material are formed, which makes the work up of this reaction very unattractive. Dark, tar-like semi-solid products are formed and yields for these particular starting materials never exceed the 50 % barrier for any substituted or unsubstituted benzamide. Yet, it represents a fast and inexpensive way to generate multi-gram quantities of the starting materials needed for the direct arylation screening reactions. The work-up is a drawback as the crude products have to be columned and then distilled under high vacuum (< 1 mbar) at temperatures higher than 100°C. For our purposes this method was used to generate large amounts of the starting materials **35**, **154** and **155**.[29]

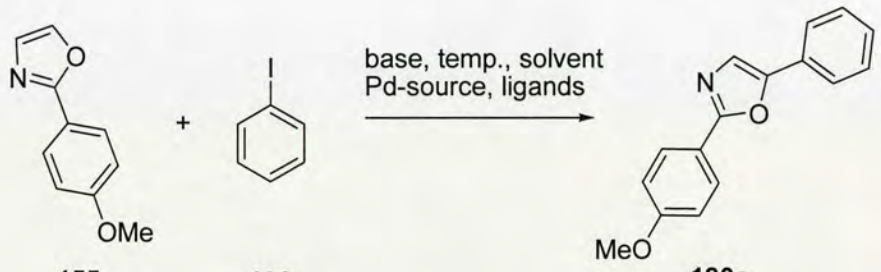


Scheme 51. 2-Phenyl-oxazole synthesis using chloroacetaldehyde and benzamide.[33]

1.5.2. Initial Screening and Optimisation

Having four starting materials in hand we set out to test the possibility of a regioselective 5-substitution. Using our most activated substrate (mechanism *vide infra*), initial attempts were commenced and results are shown in table 3.

Table 3. First direct arylation screening of organic solvents and other variables.



155 **106** **180c**

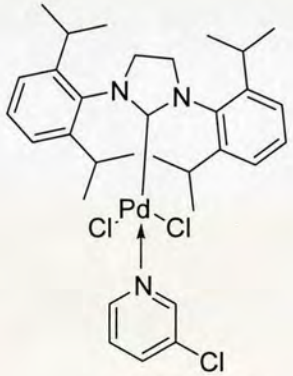
Entry	Cat.%	Base	Solvent	Pd-source	^{0}C	Product
i)	5	Ag_2CO_3	CH_3CN	$Pd_2(dba)_3$	85	20% conv.
ii)	5	Cs_2CO_3	DMF	$Pd(dppf)Cl_2$	85	SM only
iii)	20	Ag_2CO_3	Toluene	$Pd(dppf)Cl_2$	85	29% isol.
iv)	20	Ag_2CO_3	THF	$Pd(dppf)Cl_2$	85	Traces
v)	5	AgF	CH_3CN	$Pd(dppf)Cl_2$	85	65% isol.
vi)	5	AgF	CH_3CN	$Pd(OAc)_2$ / PPh_3	85	63% isol.
vii)	5	AgF	CH_3CN	PEPPSI	85	SM only
viii)	5	AgF	THF	$Pd(dppf)Cl_2$	85	Traces
ix)	5	AgF	THF	$Pd(OAc)_2$ / PPh_3	85	Traces

As in any methodology project, a screening of several organic solvents, temperatures, bases as well as ligands and Pd-sources was initiated. Early results showed that the most promising conditions were silver sources such as AgF or Ag_2CO_3 as Mori had already reported.[111] Cs_2CO_3 for example did not show any conversion of the starting materials at all. Acetonitrile, just like DMSO, being a polar solvent, produced the most successful results for these trial reactions. Unlike Mori's

communication in which he does not comment on the use of alternative palladium species, this transformation was able to be catalysed by several different palladium-sources such as Pd(dppf)Cl_2-DCM (catalyst loading 5 mol %), Pd(dppe)Cl_2, Pd(dppb)Cl_2 or Pd(OAc)$_2$ which was used together with additional PPh_3 (10 mol %).

Screening reactions were run at lower temperatures than the general direct arylation temperatures, which are generally well above 100 °C. It was the goal to find conditions far superior to previously reported conditions. Ambient temperature, if possible, would be the ultimate goal, but for screening purposes, slightly elevated temperatures were evaluated. Additionally, catalyst loadings were generally higher than desired. It was the aim to begin to screen for optimum conditions using 10 mol % of catalyst - but if possible - to decrease this amount to the smallest possible value, while still getting maximum turn-over numbers (TON's).

Initial screening experiments did not show any effect of *N*-heterocyclic carbenes, such as PEPPSI (**156**), to promote the conversion of the starting materials. No products were observed in any of the reactions when PEPPSI was used.



PEPPSI-S*i*Pr

156

Figure 11. Structure of NHC-based catalyst PEPPSI-SIPr.

As seen in table 3, early conditions reported 85 °C in acetonitrile with a couple of useful palladium-sources, such as Pd(dppf)Cl_2. Reaction times for these reactions were found to be three days (72 hrs). Interestingly, none of the reactions shown so far went to completion during this 72 hrs time span. At this point of the project, not a

single HPLC and TLC had shown full conversion. Addition of fresh catalyst, as well as ligands after 24 hrs did not improve the conversions and higher temperatures also failed to improve yields. Noteworthy is the fact, that increased temperatures actually decreased the isolated yields of these 2,5-disubstituted compounds due to the excessive formation of homo-coupled side products.

Several disubstituted compounds were generated using these conditions with yields ranging from 16 - 63 %.

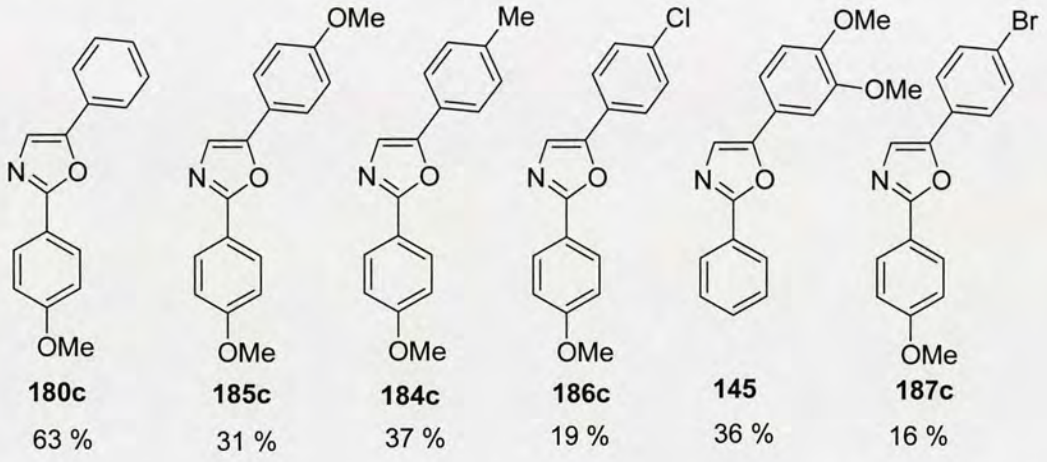


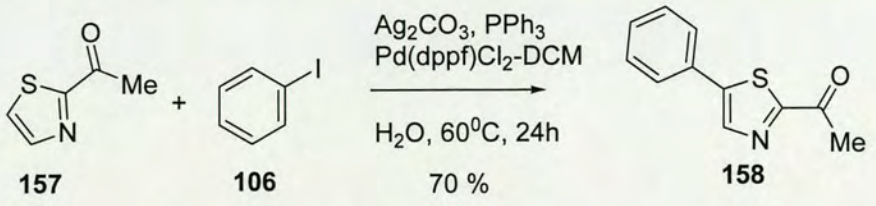
Figure 12. Isolated products and yields of early non-"on water" screening.

Microwave accelerated conditions did not show any appreciable increase in yields and were dismissed after several attempts using the most activated starting material, 2-(4-methoxy-phenyl)-oxazole (**155**) with iodobenzene.

1.5.3. On Water Direct Arylation Discovery

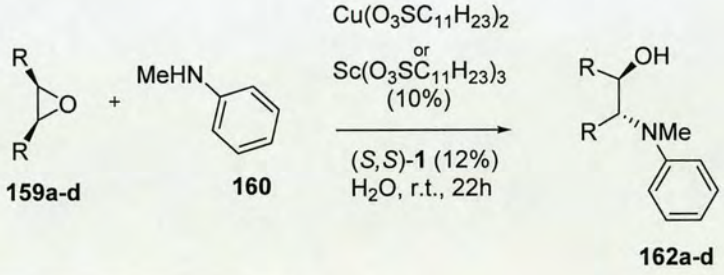
Following a rather unexpected result by a fellow student (G. Turner) working on direct arylation methodology in the Greaney group, in which thiazoles were successfully and almost quantitatively arylated with water as medium, we set out to test these conditions on oxazoles.[122] Similar conditions to the thiazole arylation were applied to the above mentioned oxazole test-reaction and showed very promising conversions on TLC and HPLC. Up to this point starting material had always be observed on TLC at $R_f = 0.2$ in 100 % DCM, but using water as "solvent" no left-

over starting materials were observed. After 24 hrs, TLC and HPLC showed full conversion of the oxazole starting material.

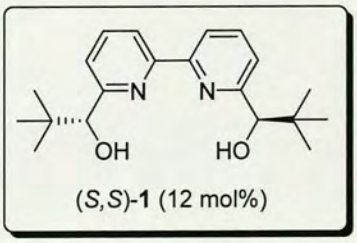


Scheme 52. Initial discovery of thiazole arylation "on water".[122]

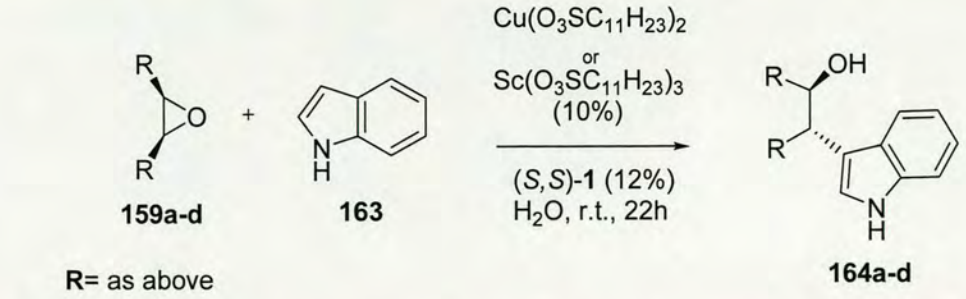
Reactions performed "in water" have a longstanding tradition and many high-profile research groups have contributed extensively to the area of organic transformation in the aqueous medium. A few selected examples are highlighted below, the works of Grieco, Breslow and Kobayashi are probably the most notable contributions to this field of research.[123-125] Several detailed reviews have highlighted the importance and need for transformations in water.[126,127]



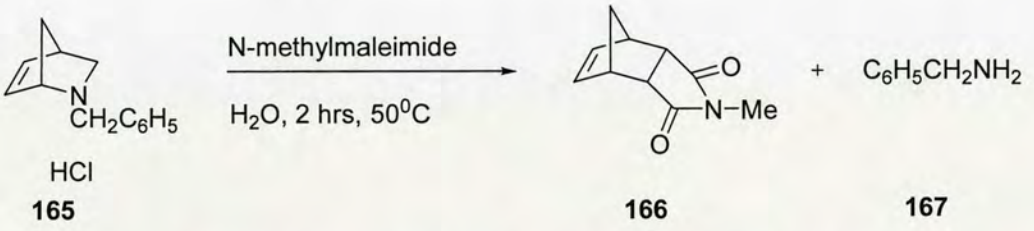
Entry	R	Cu		Sc	
		yield%	ee%	yield%	ee%
1	Ph	88	91	96	-97
2	2-Naphthyl	81	90	76	-96
3	4-MeC_6H_4	78	90	85	-96
4	4-BrC_6H_4	72	91	88	-97



161



Kobayashi's enantioselective *meso*-epoxide ring-opening reactions in water.

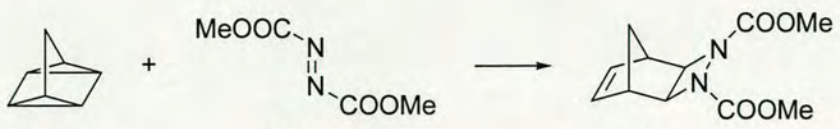


Grieco's retro aza-Diels-Alder reaction in water.

Scheme 53. Kobayashi and Grieco's work in the aqueous medium.

The term "on water"-chemistry however can only been found in the literature since 2005, when Sharpless first used it to described several organic transformations discovered in his research group, which did not dissolve in water.[128] In his communication he reported multiple organic transformations, such as the Ene-reaction, epoxide opening reactions, Claisen rearrangements (table 5), cycloadditions (table 4), as well as the Diels-Alder reaction. The reactions proceed fast, sometimes in only a few minutes, and products are obtained in excellent yields. In more detail - Sharpless reported a substantial rate acceleration when insoluble reagents are stirred in aqueous suspension, denoted in his paper as "on water" conditions. Ease of product isolation, water's unique redox stability as well as safety due to water's high heat capacity are just a few advantages over organic solvents.[129]

Table 4. Quadricyclane and dimethylazodicarboxylate-cycloaddtion solvent screening.



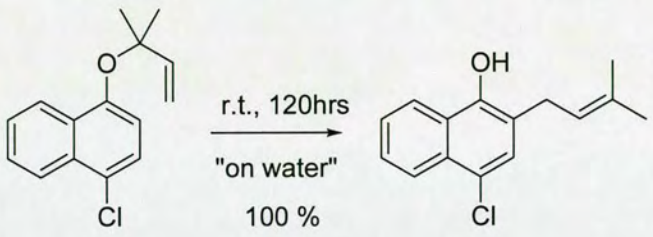
168 **169** **170**

Solvent	Time to completion
Toluene	>120 hrs
EtOAc	>120 hrs
CH_3CN	84 hrs
DCM	72 hrs
DMSO	36 hrs
MeOH	18 hrs
Neat	48 hrs
On D_2O	45 mins
On C_6F_{14}	36 hrs
On H_2O	10 mins
MeOH:H_2O (3:1) homogeneous	4 hrs
MeOH:H_2O (1:1) heterogeneous	10 mins
MeOH:H_2O (1:3) heterogeneous	10 mins

Interestingly Sharpless reported that: "...under homogenous conditions, polar protic solvents accelerate the reaction, with observed reaction rates in the following order: MeOH:H_2O (3:1) > MeOH > DMSO > $CH_3CN \approx CH_2Cl_2$ > EtOAc ≈ toluene.[130] This trend suggests that hydrogen bonding, charge stabilisation and dipolar effects may be important for rate acceleration.[131] While water contributes to such properties in homogeneous mixtures, heterogenicity was crucial for observing large rate accelerations. Thus, the presence or absence of methanol in a heterogeneous mixture made little difference, but the rate slowed considerably when enough methanol was used to make the reaction homogeneous. However, heterogenicity in itself is not responsible for the rate acceleration as the reaction "on" perfluorohexane was only slightly faster than the neat reaction."

Further studies by Sharpless also provided insight into the aromatic Claisen rearrangement.

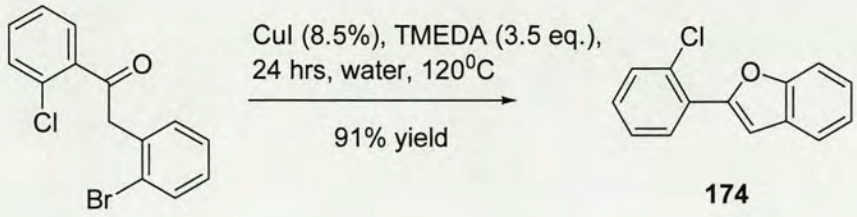
Table 5. "On water" Claisen rearrangement as described by Sharpless.[128]



171 **172**

Solvent	Yield
Toluene	16 %
DMF	21 %
CH_3CN	27 %
MeOH	56 %
neat	73 %
on H_2O	**100 %**

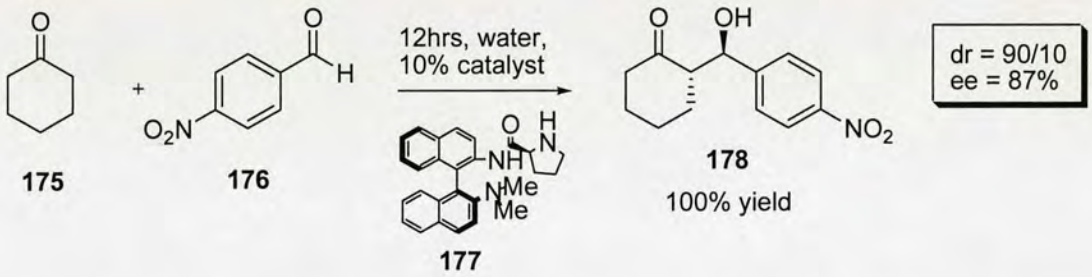
Other, more recent examples of "on water" chemistry have been published. Compounds such as 2-alkyl and 2-aryl-benzofurans can be generated via an intramolecular *O*-arylation using a Cu / TMEDA complex.[132]



173 174

Scheme 54. Synthesis of benzofurane analogues using on water techniques.[132]

In addition, Guizzetti *et al.* have shown that "on water" conditions are useful in the preparation of chiral *β*-hydroxy ketones via an enantioselective direct Aldol-reaction using 1,1'-binaphthyl-2,2'-diamine-based (S)-prolinamides.[133]



175 176 177 178

100% yield

Scheme 55. Enantioselective direct Aldol-reaction on water.[133]

The role of water in different reaction systems is best described as diverse. Some authors highlight the hydrophobic interactions of water and organic molecules. The interactions which come from the immiscibility of organic compounds in water can bring the molecules closer together, however, this alone can not be responsible for the rate acceleration as shown in Sharpless' experiments. Possible hydrogen-type bonds have been suggested and a theoretical computational study by Jung and Marcus support the hypothesis.[134,135] The authors suggest that the immense "on water" acceleration is possibly due to the ease of free OH-groups of interfacial water molecules to form H-bonds with the H-bond accepting groups in the transition state compared with that of the reactants. This lowers the activation barrier (in this case

Sharpless' examples were used for the computational study) and therefore the rate of the transformation is increased.

Our early attempts to arylate oxazoles using water gave products in yields ranging from 50 - 76 %. We did not see the need of adding extra PPh_3 to the reaction mixture as the palladium source already had ligands in place and Pd^0 must be the active catalyst for this transformation. It seemed unnecessary to add additional phosphine at the time, but practical experiments showed, that with the addition of 10 % of PPh_3, the reactions go to completion. Without PPh_3, yields dropped by as much as 40 %.

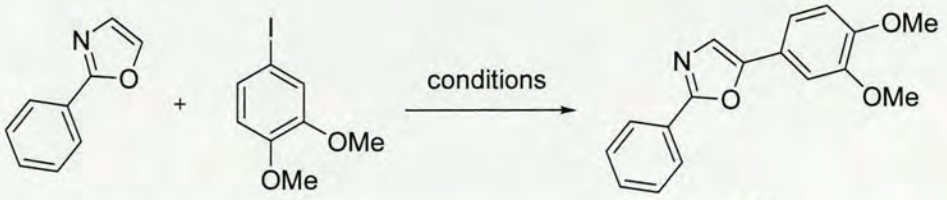
It is worth pointing out that it is rather unusual to see transition metals such as palladium catalyse sp^2-sp^2 carbon-carbon bond formations on water. Most cross coupling reactions do indeed work in very polar solvents such as DMF, but water as a medium has never been shown to promote any direct arylation reaction until the discovery in the Greaney group.

Given these exciting results, a further screening of palladium sources and ligands was initiated and aimed to investigate the general applicability of using palladium catalysts in an aqueous environment. Results of this screening reflected the earlier screening in organic solvents in which several palladium sources such as $Pd(dppb)Cl_2$ or $Pd(dppe)Cl_2$ were shown to promote the formation of 2,5-diarylated oxazoles.

The starting oxazole used for the screening was 2-phenyl-oxazole (**35**) as we decided to screen our ligands and palladium sources against an inactivated oxazole. The reaction of 2-phenyl-oxazole with 3,4-dimethoxyiodobenzene would then yield the natural product balsoxin (**145**), a target compound envisioned by us previously.

The optimised conditions turned out to be as follows:

Aryloxazole (1 eq.), aryliodide (1.2 eq.), base (Ag_2CO_3 or AgF, 2.0 eq.), 10 mol % of PPh_3, 5 mol % of $Pd(dppf)Cl_2$-DCM, 60°C – 16 hrs, water.



35 **179** **145**

Scheme 56. Generalised reaction scheme for the 5-arylation to generated balsoxin.

The direct arylation reactions described in this thesis using water as a medium are not concentration dependent (in a solution sense) as all components are immiscible in water. Several control experiments were performed to ensure all the components for the direct arylation reaction are crucial and are used in correct amounts. First of all a water-soluble base was used to see if an increase or decrease in yield would occur. K_2CO_3 and Cs_2CO_3 as base were used (even though it is known from the previous screening that a silver-source seems essential) and provided yields not exceeding the 20 % barrier. These results were somewhat expected as it seems that starting materials as well as products have to be insoluble for this reaction to occur. These "on water" reactions are highly concentrated and this concentration effect certainly plays a major role. Sharpless originally termed heterogeneous reactions using water as "on water" in his landmark paper in 2005 as described earlier in this document.[128]

In our "on water" direct arylations, a silver mirror can be observed after a few hours of heating at slightly elevated temperatures indicating the formation of AgI which itself is also insoluble in water possibly driving the reaction towards the side of the products.

Several reactions were also carried out without triphenyphosphine as an extra ligand. Triphenylphosphine turns out to be one of the key factors for this kind of chemistry to occur and when omitted, reactions rarely produce yields higher than 50 – 60 %, compared to sometimes near quantitative yields when triphenylphosphine is used.

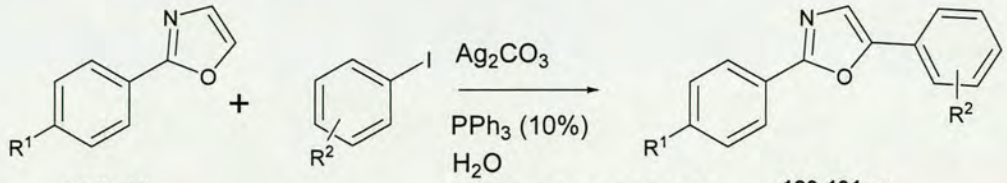
During the course of this project the mol % of palladium catalyst was also modified. As none of the reactions gave > 99 % isolated yields we already suspected a decrease

in palladium catalyst to significantly drop the yields. Nevertheless we decreased the catalyst loading from 5 mol % to 1 mol % and observed a steep decrease in yields, as expected. As a last modification we decided to decrease the equivalents of base from two equivalents (actually four equivalents) to 0.5 equivalents (actually one equivalent) and also observed a severe decrease in isolated yields for these reactions.

A wide range of 2,5-diarylated oxazoles was generated using the above described optimised conditions and are presented in Table 6. The choice of aryliodides should be discussed at this point. Emphasis was put on a highly diverse library of compounds, ranging from electron donating to electron withdrawing, sterically demanding and even substrates with a potential additional functional handle for further modification of the products.

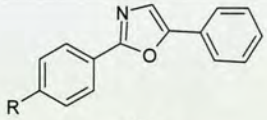
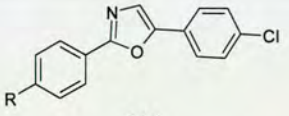
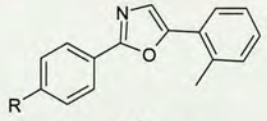
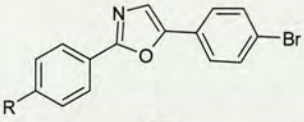
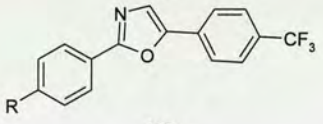
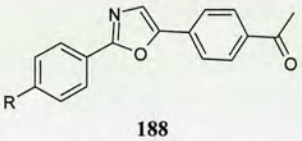
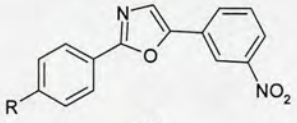
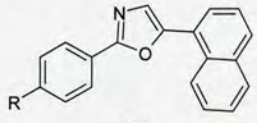
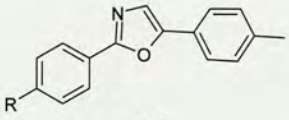
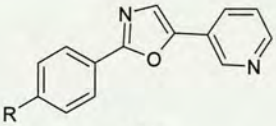
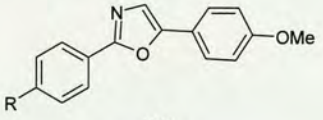
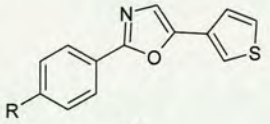
Table 6 shows a range of products. Iodobenzene for example, could be coupled in high yields; electron-donating groups such as *p*-methoxy-iodobenzene and the weaker electron donating *p*-methyl-iodobenzene could also be attached in good yields. In addition the sterically hindered *o*-methyl-iodobenzene and 1-naphthyliodobenzene were highly successful and show the strength of this methodology. Compounds such as *p*-bromo and *p*-chloro-iodobenzene are shown to react in good yields as well, giving the compounds a remaining reactivity towards further modifications such as Suzuki reactions or iron-catalysed alkylations.[136,137] The acetophenone moiety of **188** could also act as an electrophilic site that could be further modified. Examples of electron-withdrawing groups such as *p*-trifluoromethy-iodobenzene and *m*-nitro-iodobenzene have been explored. The nitro species does not work as clean as expected, very likely due to side reactions that occur, which make the purification significantly more difficult than any of the other examples.

Table 6. Overview of 36 membered library of palladium-catalysed direct arylations to generate 2,5-disubstituted oxazoles.



35 (R=H)
154 (R=Me)
155 (R=OMe)

180-191a-c
a: (R=H)
b: (R=Me)
c: (R=OMe)

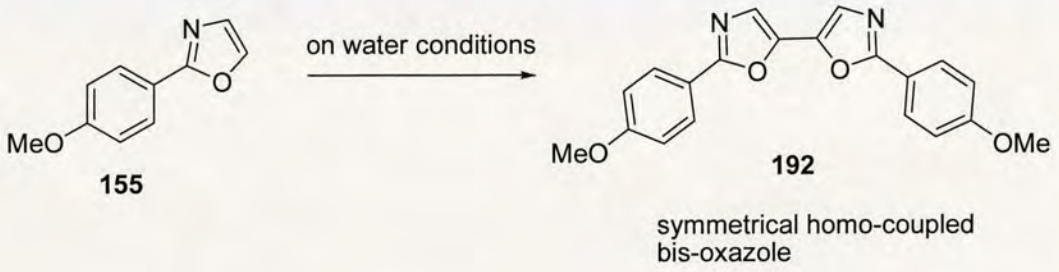
Entry	Products	Yield (%)[a]	Entry	Products	Yield (%)[a]
1	 **180**	a) 92 b) 83 c) 92	7	 **186**	a) 90 b) 87 c) 92
2	 **181**	a) 83 b) 98 c) 90	8	 **187**	a) 68 b) 83 c) 70
3	 **182**	a) 80 b) 97 c) 82	9	 **188**	a) 86 b) 89 c) 93
4	 **183**	a) 84 b) 85 c) 80	10	 **189**	a) 85 b) 76 c) 81
5	 **184**	a) 75 b) 84 c) 97	11	 **190**	a) 33[x] b) 30[x] c) 36[x]
6	 **185**	a) 76 b) 89 c) 79	12	 **191**	a) traces b) traces c) traces

a= phenyl, b= *p*-Me, c= *p*-OMe
[a] Isolated yield after SiO_2 chromatography.
[x]= oxazole homocoupling observed, probably due to slow oxidative addition of aryliodide.

Lastly one should mention the heteroaromatic substrates used in this report. It turned out to be rather difficult to isolate the thiophene (**191**) and pyridine (**190**) examples. The 3-iodothiophene was simply too reactive and gave TLC plates that showed up to 9(!) new spots, most of them highly fluorescent under long and short wavelength

UV-light. Purification of the thiophene substrates was simply not possible as no major spot was observed, the TLC was uninterpretable (several different mobile phases) and any attempts of actually purifying the mixture gave no spot that had any isolated mass (weight).

The pyridine substrates are a different story, it was possible to isolate the products in very moderate yields but to our surprise we also isolated homo-coupling products. Surprising is the fact that we did not isolate homo-coupling products of the aryliodides as it is normally the case but homo-coupling of the oxazole species.



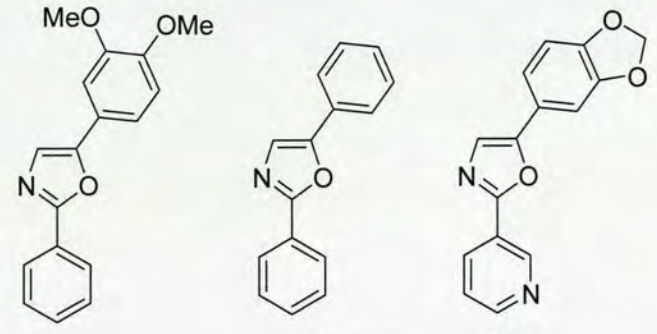
Scheme 57. Homo-coupling of the oxazole starting materials.

This is rather unusual and highly interesting as the mechanism for this transformation is not trivial and will have to be further investigated in our laboratory. We have not investigated this phenomenon in great detail but early results show that only the most activated oxazole species (such as the very electron-rich 2-(4-methoxy-phenyl)-oxazole (**155**) are able to homo-couple under these conditions. Interestingly, even without palladium catalyst, we see a small amount of this product formed. No reaction does however occur if both, silvercarbonate and the palladium catalyst are left out, suggesting a role of the silver salt.

To strengthen the utility of this direct arylation approach using water we decided to prove the concept on two small natural products, texaline and balsoxin.

Balsoxin (**145**) and texaline (**36**) were both successfully synthesised in 84 % and 74 %, respectively. In addition, an industrially useful scintillator (2,5-diphenyl-oxazole,

180a) was also synthesised in 92 % yield, showing the effectiveness and versatility of this methodology.



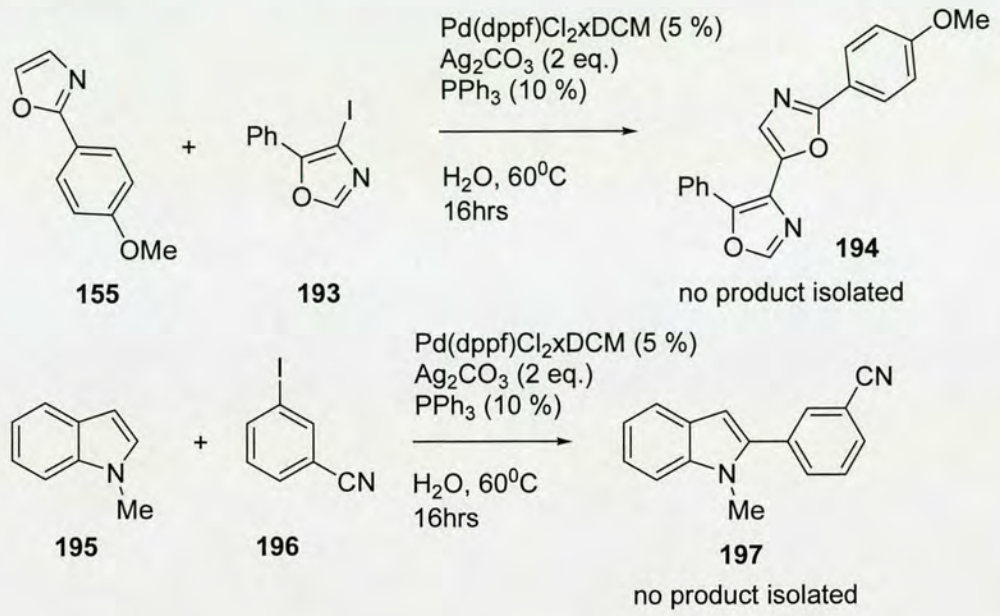
145 Balsoxin | **180a** 2,5-Diphenyl-oxazole | **36** Texaline

Scheme 58. Balsoxin, 2,5-diphenyl oxazole (scintillator) and texaline.

Work-up of the above-described reactions is a simple filtration through celite or a filter fitted with a frit, followed by several washings with DCM. The resulting bi-phasic mixture can then simply be extracted after addition of some extra water to make the phase separation visible and then the organic phase is dried with $MgSO_4$, filtered and solvent evaporated under reduced pressure. These optimised reactions can almost be looked at as 'neat' as the high reactivity of the starting materials bases itself on the close, almost molten, proximity of all starting materials in the reaction vessel. Water in this case acts as a medium absorbing the heat that is put into the system. If the reaction is done without water, the yields only drop a few percent, proving that there is no real solvent-effect promoting these reactions using water.

In addition to the direct arylations described above initial attempts to generate bis-oxazoles have been tried but did not succeed at this point (scheme 59). The product of this particular reaction would be a very interesting bis-oxazole (**194**) with a rare oxazole substitution pattern, which has not been shown to this day. Unfortunately this reaction does not work, small amounts of what could be product (due to the very distinct UV-activity) are seen on TLC but are not able to be isolated via column chromatography. Mostly starting material is re-isolated in this case. The steric-effect of the phenyl group right next to the iodine might be a reason why this reaction does not proceed in good yields, as well as the heteroaromatic nature of the oxazole. One

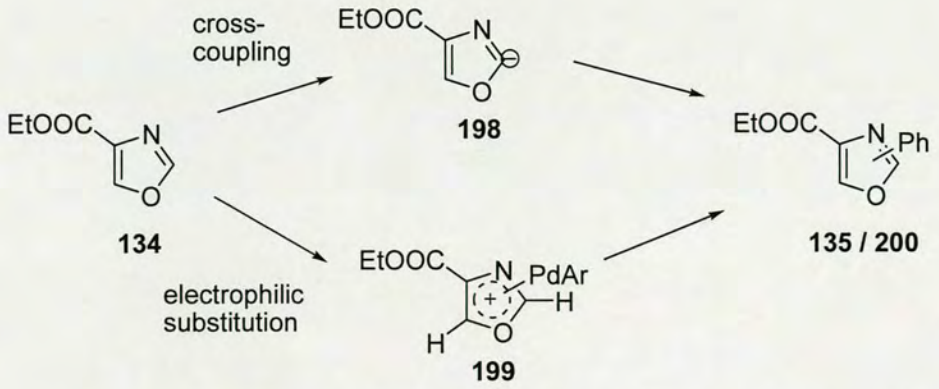
could also expect to maybe see some coupling between the iodine and the vacant 2-position of the oxazole but this has to be investigated in the future and so far has not been observed.



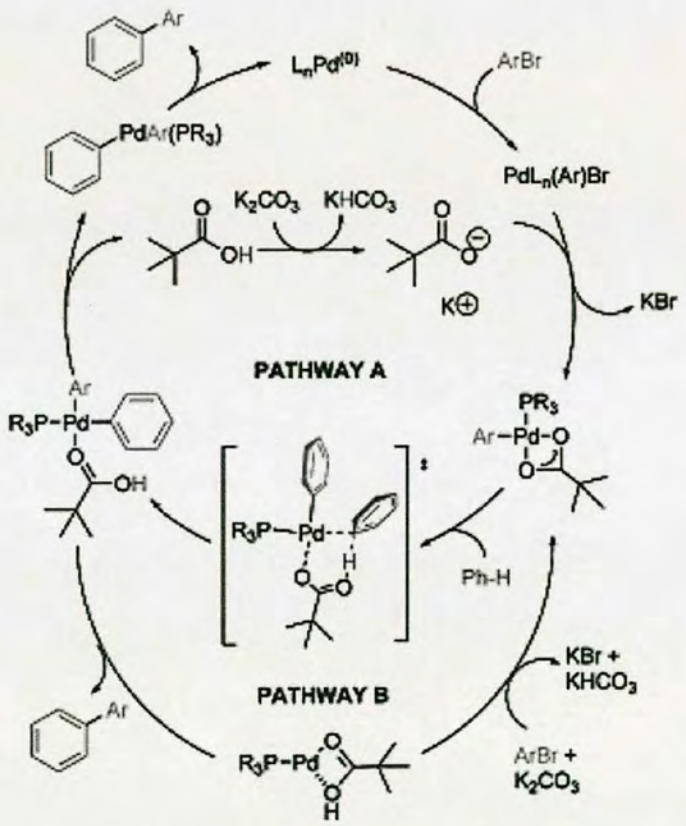
Scheme 59. Initial attempts to generate bis-oxazoles and 2-arylated indoles using our methodology failed.

1.5.4 Mechanism

The mechanism involved in the arylation of azoles and heterocycles in general has raised some interest over the last few years. Mechanistically, the direct arylation reaction of heterocycles is thought to occur primarily via three possible routes: (1) an electrophilic aromatic substitution, (2) a carbanion cross-coupling mechanism or (3) a palladium-pivalic acid co-catalysed mechanism as proposed by Fagnou and coworkers.[138-140] The arylation on the 5-position of oxazole is believed to be of an electrophilic substitution nature rather than a cross coupling. Different proposals have been put forward for the arylation of the 2-position of oxazole. The main mechanisms are discussed in detail below.



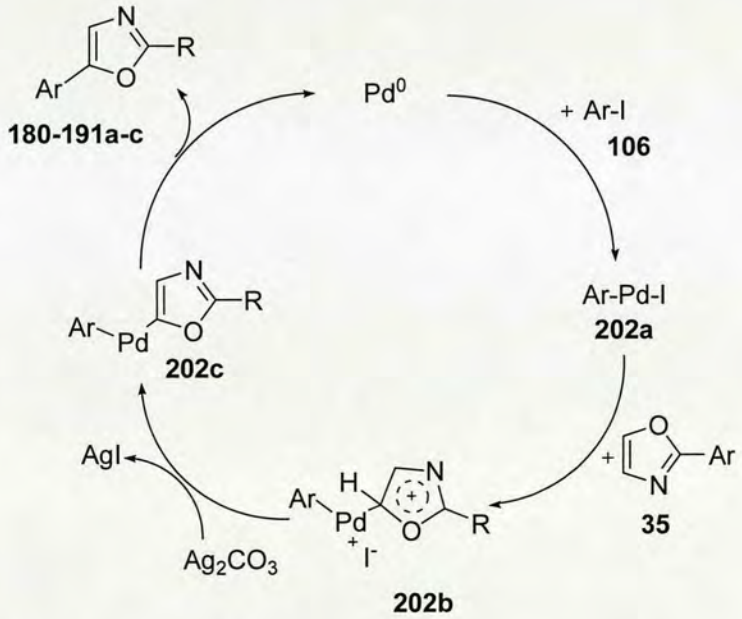
Scheme 60. Possible mechanistic pathways for the direct arylation of heterocycles.[138-140]



Scheme 61. Mechanism for the arylation of aromatic or heteroaromatic compounds as suggested by Fagnou *et al.*[140]

Early work by Miura in 1998 suggests that the arylation reactions of 1,3-azoles are of an electrophilic character. Miura's report is the first in which the mechanism of the arylation of azoles is discussed in detail.[138] Miura comments on the use of palladium

and copper, the ladder promoting the arylation on the acidic 2-position of oxazoles and thiazoles. When palladium is used by itself, or as a co-metal together with Cu^{I} sources, the 5-position is preferentially arylated in good yields. Further, the authors rank the C-H bonds on azoles in order of highest electron density, showing that the most electron rich atom is C5, followed by C4 and then C2.[141] Most interesting are the experimental results performed by Miura *et al.*, the authors attempt the same direct arylation reaction but using differently substituted azoles, showing that electron donating effects of substituents have a direct effect on the obtained yields of the reactions.[138] As expected, the most electron-rich examples give the highest yields and deactivated azoles tend to react slower. These results further support the proposed mechanism. It should further be noted that Miura suggests that the electrophilic mechanism is very feasible for the 5-position of thiazoles and imidazoles as these positions are most electron-rich. It can only be speculated that the electron-poor 2-position reacts via a similar mechanism.

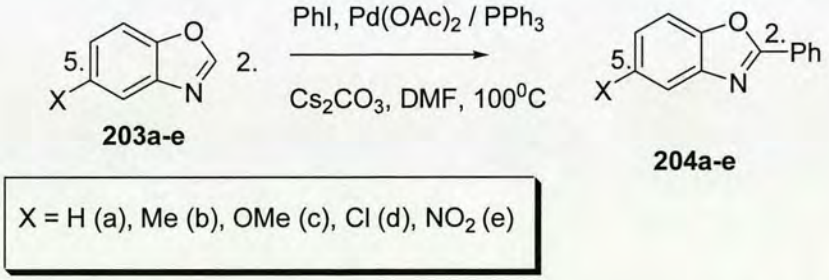


Scheme 62. Mechanism put forward by Miura and co-workers.

As a first step, the palladium inserts itself into arylhalide bond via an oxidative addition known from other palladium catalyzed reactions such as the Stille or Suzuki for example. Then the lone pair from the oxygen of the oxazole can be viewed as the

initiator of a flow of electrons around the ring of oxazole to then generate a carbon-palladium bond and a Wieland intermediate. The base then abstracts a proton α- to the cationic oxygen of this Pd^{II} species to regenerate its aromaticity. Reductive elimination as the last step of this transformation generates the product in a 2,5-disubstituted fashion and allows the palladium catalyst to continue its cycle as Pd^0. Some additional work involving CuI as a co-catalyst has been disclosed by Hoarau and co-workers promoting the initially proposed mechanism by Miura.[142,143]

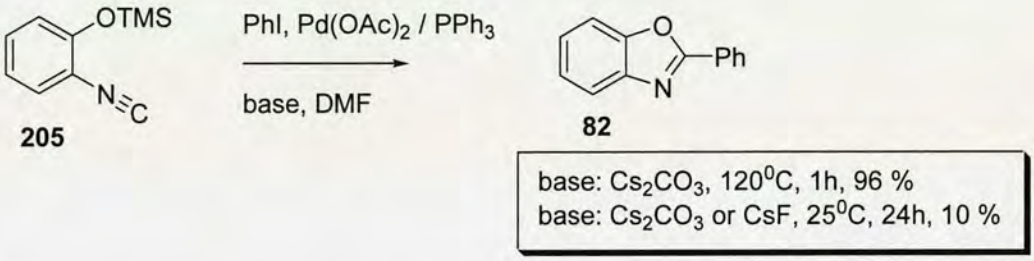
Interestingly, several years later, Zhuravlev and Sanchez communicated a very detailed study on the mechanism of the C2 arylation of benzoxazole.[144] The authors provide strong evidence for a ring-opening pathway in the palladium-catalysed direct arylation of benzoxazoles. A set of kinetic experiments on a series of benzoxazoles was performed using Hammett studies, which offer the opportunity to probe the electronic demand of Pd-catalysed arylation by having different substituents at the C-5 position of benzoxazole ring. Using several electronically different benzoxazoles, a linear effect was shown, with 5-methoxy on the slow end of the rate of reaction, and 5-nitrobenzoxazole on the fast side. 5-Nitrobenzoxazole arylated at room temperature showing the increase in rate of arylation using this electron-withdrawing group.[144]



Scheme 63. Effect of substituents on the rate of 2-arylation of benzoxazole.[144]

Key experiment in this communication is the use of 2-trimethylsiloxyphenyl isocyanide as a precursor to the active phenolate, which will be produced *in situ* via addition of CsF to deprotect the hydroxy group. The arylation reaction then occurs in less than one hour at 120 °C, giving rise to the ring-closed 2-arylated benzoxazole

(**204**). The reaction also takes place at room-temperature, but at a slower rate (24 hrs, 10 % yield).



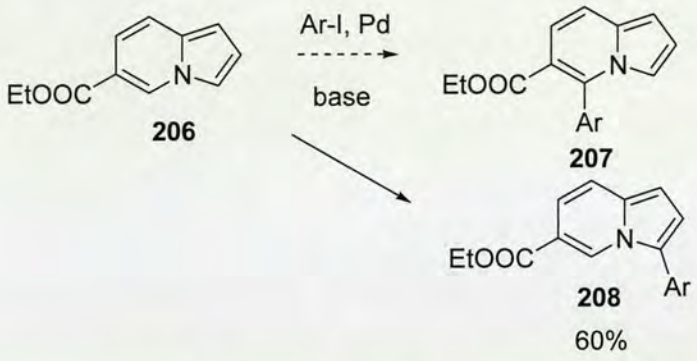
Scheme 64. Transformation of ring-opened OTMS-analogue **205** to 2-phenylbenzoxazole **82**.[144]

Zhuravlev argues that based on these above results, the direct arylation on the 2-position of benzoxazoles is inconsistent with the electrophilic mechanism proposed by earlier studies. The generation of an isocyanophenolate is reported as a key step and the control of the C-H acidity on the 2-position is anticipated to be a very important element in developing a possible mild arylation method.

Detailed computational data calculating the activation barriers for each of the steps in the catalytic cycle is provided and supports the anionic mechanism in which a Pd-isocyanide complex is formed first, followed by an intramolecular cyclisation of the phenolate oxygen to generate the Pd-benzoxazole system. This cyclisation step has an activation barrier of around 3 kcal / mol, which in comparison, is much less than the strength of a hydrogen-bond, which lies at about 5-10 kcal / mol.

Lastly, a thorough study on the mechanism of indolizines should be mentioned in brief as the authors followed a similar thought process in their work. In short, several different mechanistic paths such as a Heck reaction, a C-H activation, a cross-coupling as well as an electrophilic substitution were considered to be possible for the 3-arylation of indolizines. This research is of interest to the mechanistic discussion of oxazole 5-arylation because final arguments in this paper once again evolve around the effect that substituents have on the isolated yields.[145] It seems that the direct comparison between electronic effects and yields is once again a viable

argument. A very interesting experiment by Gevorgyan is shown in scheme 64 where a reaction having the possibility to react via a Heck-type mechanism or via an electrophilic mechanism is set up. Results show a clean reaction generating only one single regioisomer, on C3, not on C5 where a Heck-type product would be expected.



Scheme 64. Attempts to perform Heck reaction on indolizine **206**.[145]

The authors then take a further step to understand and support the mechanism by providing a screening table of electron neutral and electron withdrawing substituents on the position adjacent of where the arylation occurred. Relative rates are clearly influenced by the substituents and show a decrease in reactivity when the electron withdrawing power of the substituent is superior. This finding supports the existence of an 'electrophilic substitution' mechanism further.

We would like to further note that the direct arylation on 2-aryl-substituted oxazoles could technically yield two products, a 2,4-diarylated as well as a 2,5-diarylated oxazole. Spectroscopically these two regioisomers are very similar and can only be distinguished from each other when compared to literature values - should these exist. Molecular weight differences as well as combustion analyses also do not provide the means to decide which isomer is formed. Theoretically, based on the mechanism postulated above, one should expect to obtain the 2,5-diarylated oxazole. This is indeed true as we were lucky enough to grow crystals of one of the synthesised compounds. Figure 13 provides a top / bottom view of one of the pyridine analogues synthesised. The compound shown is 2-(4-methyl-phenyl)-5-(3-pyridyl)-oxazole (**190b**). Having obtained a crystal structure in addition to matching

texaline and balsoxin to literature NMR data provides us with strong proof that indeed the 2,5-diarylated compounds have been synthesised.

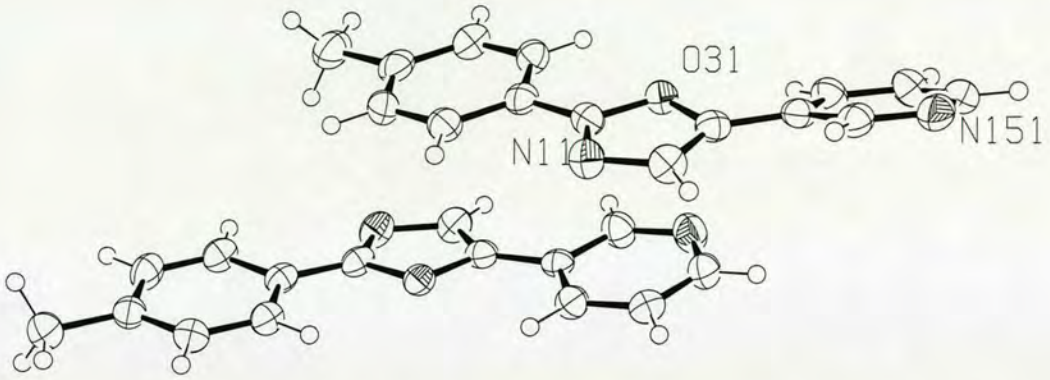


Figure 13. X-ray top / bottom view of a selected 2,5-diarylated oxazole (**190b**).

1.6. Summary

In conclusion, a robust method to generate 2,5-disubstituted oxazoles has been developed and it has been shown that a large range of substrates can be generated from electron rich to electron poor, sterically hindered and even some heteroaromatic. The methodology has been taken a step further and two natural products showing antimycobacterial activity have been synthesised in good to excellent yields. No competing substitution reaction at the 4-position has been observed and the amount of aryliodide homo-coupling is kept at an absolute minimum compared to reactions done in organic solvents where homo-coupling has been observed.

It seems that the water represents a viable platform (as all components are insoluble in water) to allow a highly concentrated reaction to occur in a shorter period of time as the formed iodide is also insoluble in water. The use of water can also be described as somewhat "green chemistry" even though one should remember that the work-up still involves several washings with DCM. Modern methods to generated such compounds via direct arylation are among the 'Wanted List' of many

pharmaceutical companies.[146] Given the lack of solubility of reactants, reagents and products in water, the system is an example of what Sharpless has termed an "on water" reaction, whereby the organic components react in a heterogeneous aqueous environment. The developed reactions are safer than normal organic reactions due to the use of water, which has a high heat capacity. Increased rate and therefore increased efficiency are the result of a high effective-concentration which essentially acts as the driving force for these "on water" reactions.

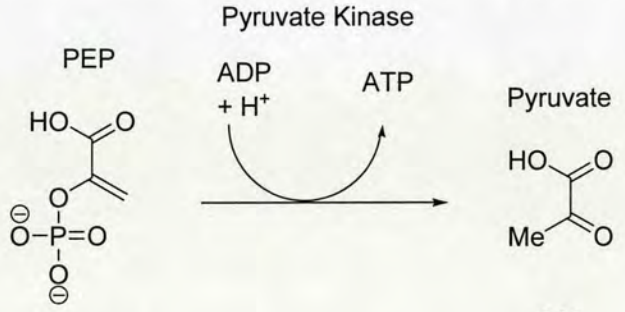
Furthermore, a few selected compounds have been sent away for biological testing (IC_{50} tests) on pyruvate kinase which catalyses the final step of glycolisis, the conversion of PEP to pyruvate with the production of one molecule of ATP.

D-Glycose
209

Pyruvate
210

atom balance is maintained by the two phosphate groups

Scheme 65. Transformation of *D*-glucose to pyruvate (Glycolisis).



211 **210**

Scheme 66. Final step of glycolisis shown in detail.

Our synthesised compounds show very similar structural features as a library of di-substituted oxadiazole compounds that have been identified via a qHTS.[147] This target is interesting as these compounds are potential new therapeutic agents for the treatment of trypaonasomiasis and leishmaniasis, tropical diseases caused by

parasites. This project is done in collaboration with the global consortium targeting the glycolytic pathway of these parasites.[148,149]

These compounds were however insoluble in the conditions required for the bioassay. No activities can be reported.

1.7 Experimental

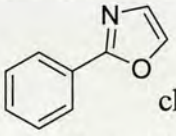
General

NMR spectra were obtained from a Brüker AC250 (250MHz) instrument and calibrated to residual solvent peaks: ^{1}H - $CDCl_3$, 7.26 ppm and ^{13}C – $CDCl_3$, 77.0 ppm. The ^{1}H-NMR data is presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet), coupling constant (J in Hz) and structural assignment. The ^{13}C-NMR data is reported as ppm on the δ scale, followed by the structural assignment. High resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using Finnigan MAT 95XP and Finnigan MAT 900XLT instruments ES analysis. The data is presented as the ionisation method, followed by the calculated and measured masses. TLC was preformed on Merck 60 F254 silica plates and visualised by UV light. Compound purification was carried out by wet flash column chromatography using Merck Kieselgel 60 (particle size 35-70). Eluent constitution is quoted as ratios or percentages. All solvents were dried before use unless otherwise stated. Anhydrous solvents were obtained from a solvent purification system supplied by www.glasscontoursolventsystems.com or a PureSolv solvent purification system supplied by Innovative Technologies Inc. All other chemicals were purchased from a chemical supplier and used as received.

General procedure for Negishi reactions: **2-*p*-Tolyl-oxazole (154)**

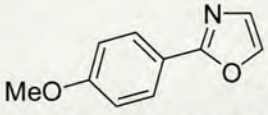
Oxazole (0.30 g, 4.41 mmol, 1.4 equiv.) was dissolved in THF (20 mL) under N_2 atmosphere at -78 °C, treated with *n*-BuLi (1.6 M in hexane, 3.35 ml, 5.35 mmol, 1.2 equiv. based on oxazole) maintaining an internal temperature below -60 °C. After stirring for 10 min, solid $ZnCl_2$ (1.20 g, 9.45mmol, 3.0 equiv.) is added portion wise to avoid clumping, the cooling bath is removed, contents warmed to room temperature. Once at ambient temperature, the catalyst $Pd(PPh_3)_4$ (0.079g, 0.22 mmol, 5 mol%) and the *p*-methyl iodobenzene (0.686 g, 3.15 mmol, 1.0 equiv) were added and the contents heated to 60 °C and stirred for four hours. The solvent was removed under reduced pressure and the contents were partitioned between aq. NH_4Cl and EtOAc. Extraction and washing with NH_4Cl, followed by $MgSO_4$ drying and filtration of $MgSO_4$, as well as column chromatography in 100 % DCM afforded product **154** as a colourless oil (0.376 g, 75 % yield). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.82-7.78 (2H, d, *J*= 6.5 Hz), 7.53 (1H, s), 7.12-7.06 (3H, m) 2.24 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.1 (quat), 140.5 (quat), 138.2 (CH), 129.4 (CH), 128.2 (CH), 126.2 (CH), 124.8 (quat), 21.4 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{10}H_9NO$ 159.0679, found 159.0676.

2-Phenyl-oxazole (35)



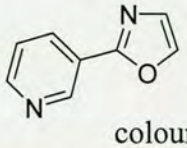
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **35** as a colourless oil (0.458 g, 83 % yield), with identical spectral data to that previously reported.[150]

2-(4-Methoxy-pheny)-oxazole (155)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave **155** as a colourless oil (0.474 g, 86 % yield) with identical spectral data to that previously reported.[121]

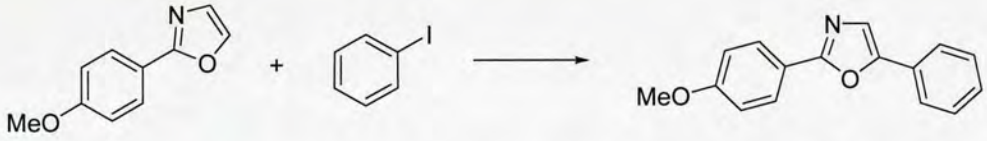
3-Oxazol-2-yl-pyridine (211)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product as a colourless oil (0.359g, 78 % yield), **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.40 (1H, d, *J*= 1.5 Hz), 8.83 (1H, dd, *J*= 4.9 Hz, 1.6 Hz), 8.46 (1H, dt, *J*= 10.1 Hz, 2.0 Hz), 7.94 (1H, d, *J*= 0.8 Hz), 7.50 (1H, m), 7.41 (1H, d, *J*= 0.8 Hz); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 159.4 (quat), 150.9 (CH), 147.5 (CH), 139.3 (CH), 133.8 (CH), 128.7 (CH), 123.8 (quat), 123.7 (CH); **HRMS** (EI) *m/z* calcd for $C_8H_6N_2O$ 146.0475, found 146.0472.

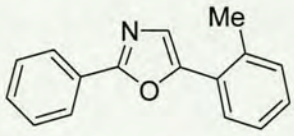
Direct Arylations. Compounds **180a**, **b** and **c**, **185a**, **b** and **c**, **186a**, **b** and **c**, **187a** and **c**, **189a** have previously been reported in the literature.[15,151]

Representative procedure: **2-(4-Methoxy-phenyl)-5-phenyl-oxazole (180c)**



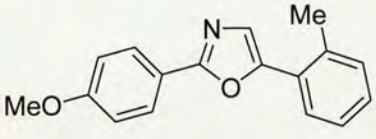
Ag_2CO_3 (317 mg, 1.15 mmol, 2 equiv.), PPh_3 (15.2 mg, 0.058 mmol, 10 mol %), Pd(dppf)Cl_2 DCM (24 mg, 5 % mol) were put into a carousel tube and mixed well. The aryl iodide (0.078 ml, 0.692 mmol, 1.2 equiv.), followed by *p*-methoxyphenyl-2-oxazole (0.101 g, 0.577 mmol, 1 equiv.) were added via pipette. Lastly 4-7 ml of distilled water was added via wash bottle and the tube was heated to 60 °C and stirred 24 hrs. The dark mixture / melt was filtered through celite using DCM and acetone to wash several times. TLC analysis showed a bright blue spot (UV 254 nm) with R_f= 0.20 (DCM, 100 %). Purification by chromatography (SiO_2, CH_2Cl_2 100 %) gave the pure product (120 mg, 83 %) with identical spectral data to that previously reported.

2-Phenyl-5-*p*-tolyl-oxazole (181a)



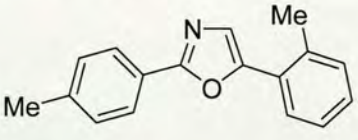
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **181a** as a white solid (113 mg, 83 % yield, Mp. 62-63 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.04-8.00 (2H, m), 7.54-7.51 (2H, m), 7.40-7.37 (3H, m), 7.31 (1H, s), 7.18-7.15 (2H, m), 2.30 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 160.7 (quat), 150.7 (quat), 134.8 (quat), 131.2 (CH), 130.3 (CH), 128.8 (CH), 127.4 (quat), 127.2 (quat), 126.7 (CH), 126.2 (CH), 21.9 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{16}H_{13}NO$ 235.0992, found 235.0993.

2-(4-Methoxy-phenyl)-5-*o*-tolyl-oxazole (181c)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM / acetone 99:1) gave the coupled product **181c** as a white solid (150 mg, 98 % yield, Mp. 71-73 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.22-8.18 (2H, m), 7.92 (1H, m), 7.45 (1H, s), 7.46-7.41 (3H, m), 7.17-7.13 (2H, m), 4.02 (3H, s), 2.68 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.2 (quat), 160.7 (quat), 150.0 (quat), 134.5 (quat), 131.0 (CH), 128.0 (CH), 127.8 (CH), 127.3 (quat), 126.4 (CH), 126.0 (CH), 125.9 (CH), 120.1 (quat), 114.1 (CH), 55.2 (CH_3), 21.8 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{17}H_{15}NO_2$ 265.1097, found 265.1094.

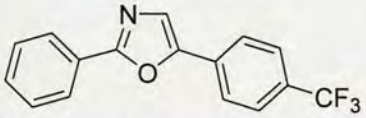
5-*o*-Tolyl-2-*p*-tolyl-oxazole (181b)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **181b** as a white solid (129 mg, 90 % yield, mp. 87-89 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.24-8.21 (2H, m), 7.99 (1H, m), 7.54-7.48 (6H, m); 2.74 (3H, s), 2.62 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.0 (quat), 150.3 (quat), 140.5 (quat), 134.7 (quat), 131.1 (CH), 129.4 (CH), 128.2 (CH), 127.3 (quat), 126.7 (CH), 126.2 (CH), 126.1 (CH), 126.0 (CH),

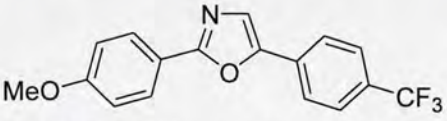
124.7 (quat), 21.8 (CH_3), 21.4 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{17}H_{15}NO$ 249.1148, found 249.1146.

2-Phenyl-5-(4-trifluoromethyl-phenyl)-oxazole (182a)



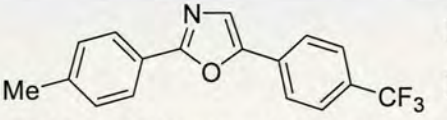
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **182a** as a white solid (134 mg, 80 % yield, Mp. 97-99 °C). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.13-8.09 (2H, m), 7.79 (2H, d, *J*= 8.2 Hz), 7.67 (2H, d, *J*= 8.2 Hz), 7.52-7.47 (4H, m); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.9 (quat), 149.7 (quat), 131.2 (quat), 130.7 (quat), 128.8 (CH), 127.0 (quat), 126.4 (CH), 125.2 (CH), 124.1 (CH)-(not all peaks assigned); **HRMS** (EI) *m/z* calcd for $C_{16}H_{10}F_3NO$ 289.0709, found 289.0708.

2-(4-Methoxy-phenyl)-5-(4-trifluoromethyl-phenyl)-oxazole (182c)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **182c** as a white solid (178 mg, 97 % yield, Mp. 132-133 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.07-8.03 (2H, m), 7.79 (2H, d, *J*= 8.2 Hz), 7.68 (2H, d, *J*= 8.7 Hz), 7.50 (1H, s), 7.02-6.98 (2H, m), 3.88 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.1 (quat), 161.7 (quat), 149.3 (quat), 131.4 (quat), 128.2 (CH), 125.1 (CH), 124.0 (CH), 119.8 (quat), 114.3 (CH), 55.4 (CH_3)-(not all peaks assigned); **HRMS** (EI) *m/z* calcd for $C_{17}H_{12}F_3NO_2$ 319.0815, found 319.0812.

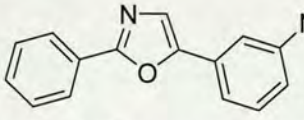
2-*p*-Tolyl-5-(4-trifluoromethyl-phenyl)-oxazole (182b)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **182b** as a white solid (144 mg, 82 % yield, Mp. 98-100 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.02-7.99 (2H, m), 7.80 (2H, d, *J*= 7.5 Hz), 7.67 (2H, d, *J*= 7.5 Hz), 7.53 (1H, s), 7.32-7.28 (2H, m), 2.35 (3H, s); **^{13}C**

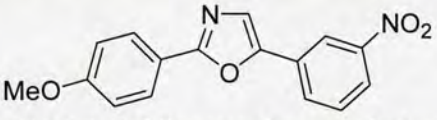
NMR (63 MHz, $CDCl_3$) δ 162.2 (quat), 149.5 (quat), 141.1 (quat), 131.3 (quat), 129.6 (CH), 126.4 (CH), 125.1 (CH), 124.3 (quat), 124.1 (CH), 21.6 (CH_3)-(not all peaks assigned); **HRMS** (EI) *m/z* calcd for $C_{17}H_{12}F_3NO$ 303.0866, found 303.0867.

5-(3-Nitro-phenyl)-2-phenyl-oxazole (183a)



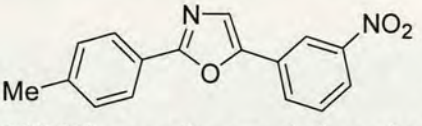
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave **183a** as a pale yellow solid (129 mg, 84 % yield, Mp. 145-147 °C). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.53 (1H, t, *J*= 1.9Hz), 8.19-8.10 (3H, m), 8.00 (1H, m), 7.63 (1H, m), 7.59 (1H, s), 7.52-7.49 (3H, m); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.1 (quat), 148.9 (quat), 148.8 (quat), 130.9 (CH), 130.0 (CH), 129.6 (quat), 129.5 (CH), 128.9 (CH), 126.8 (quat), 126.5 (CH), 125.5 (CH), 122.7 (CH), 118.8 (CH); **HRMS** (EI) *m/z* calcd for $C_{15}H_{10}N_2O_3$ 266.0686, found 266.0687.

2-(4-Methoxy-phenyl)-5-(3-nitro-phenyl)-oxazole (183c)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **183c** as a yellow solid (145 mg, 85 % yield, Mp. 196-198 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.53 (1H, t, *J*= 1.8 Hz), 8.17 (1H, m), 8.09-8.06 (2H, m), 8.00 (1H, m), 7.62 (1H, t, *J*= 7.5 Hz), 7.56 (1H, s), 7.04-7.00 (2H, m), 3.89 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.8 (quat), 148.8 (quat), 148.4 (quat), 130.0 (CH), 129.8 (quat), 129.4 (CH), 128.3 (CH), 128.2 (quat), 125.3 (CH), 122.5 (CH), 119.6 (quat), 118.7 (CH), 114.4 (CH), 55.5 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{16}H_{12}N_2O_4$ 296.0792, found 296.0790.

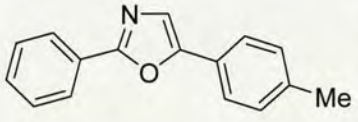
5-(3-Nitro-phenyl)-2-*p*-tolyl-oxazole (183b)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **183b** as a pale yellow solid (129 mg, 80 % yield,

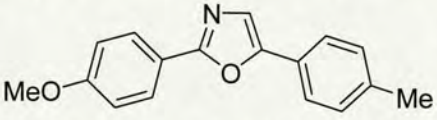
Mp. 157-159 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.55 (1H, t, *J*= 2.0 Hz), 8.15 (1H, m), 8.02-7.97 (3H, m), 7.61 (1H, t, *J*= 8.3 Hz), 7.56 (1H, s), 7.32-7.26 (2H, m), 2.43 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.4 (quat), 148.7 (quat), 148.5 (quat), 141.3 (quat), 130.0 (CH), 129.7 (quat), 129.6 (CH), 129.4 (CH), 126.5 (CH), 125.4 (CH), 124.1 (quat), 122.6 (CH), 118.7 (CH), 21.5 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{16}H_{12}N_2O_3$ 280.0842, found 280.0843.

2-Phenyl-5-*p*-tolyl-oxazole (184a)



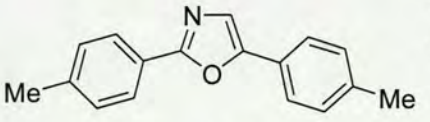
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **184a** as a white solid (102 mg, 75 % yield, Mp. 74-75 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.04-8.00 (2H, m), 7.55-7.51 (2H, m), 7.40-7.37 (3H, m), 7.31 (1H, s), 7.18-7.15 (2H, m), 2.30 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.8 (quat), 151.5 (quat), 138.5 (quat), 130.2 (CH), 129.6 (CH), 128.8 (CH), 127.5 (quat), 126.2 (CH), 125.3 (quat), 124.1 (CH), 122.8 (CH), 21.3 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{16}H_{13}NO$ 235.0992, found 235.0994.

2-(4-Methoxy-phenyl)-5-*p*-tolyl-oxazole (184c)



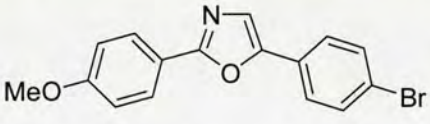
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **184c** as a white solid (149 mg, 97 % yield, Mp. 102-104 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.98-7.94 (2H, m,), 7.53-7.50 (2H, m, 7.27 (1H, s), 7.18-7.14 (2H, m), 6.93-6.89 (2H, m), 3.79 (3H, s), 2.31 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.3 (quat), 160.9 (quat), 150.9 (quat), 138.2 (quat), 129.5 (CH), 127.9 (CH), 125.4 (quat), 124.0 (CH), 122.5 (CH), 120.3 (quat), 114.2 (CH), 55.4 (CH_3), 21.3 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{17}H_{15}NO_2$ 265.1097, found 265.1096.

2,5-Di-*p*-tolyl-oxazole (184b)



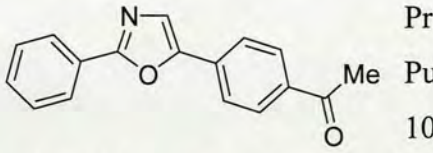
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **184b** as a white solid (140 mg, 97 % yield, Mp. 106-107 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.19 (2H, d, *J*= 8.3Hz), 7.80 (2H, d, *J*= 7.8Hz), 7.57 (1H, s), 7.45-7.41 (4H, m), 2.60 (3H, s), 2.58 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.0 (quat), 151.1 (quat), 140.4 (quat), 138.3 (quat), 129.5 (CH), 129.4 (CH), 126.1 (CH), 125.3 (quat), 124.8 (quat), 124.0 (CH), 122.6 (CH), 21.4 (CH_3), 21.3 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{17}H_{15}NO$ 249.1148, found 249.1147.

5-(4-Bromo-phenyl)-2-(4-methoxy-phenyl)-oxazole (187c)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **187c** as a white solid (158 mg, 83 % yield, Mp. 137-139 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.03-7.99 (2H, m), 7.53 (4H, s), 7.38 (1H, s), 6.99-6.96 (2H, m), 3.85 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.4 (quat), 149.6 (quat), 132.0 (CH), 127.9 (CH), 127.0 (quat), 125.4 (CH), 123.7 (CH and quat), 121.9 (quat), 119.9 (quat), 114.2 (CH); **HRMS** (EI) *m/z* calcd for $C_{16}H_{12}BrNO_2$ (Br^{79}) 329.0046, found 329.0060, calcd for $C_{16}H_{12}BrNO_2$ (Br^{81}) 331.0026, found 331.0009.

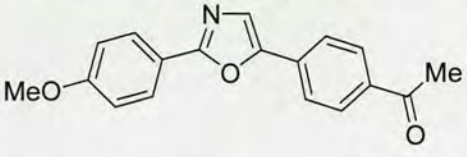
1-[4-(2-Phenyl-oxazol-5-5-yl)-phenyl]-ethanone (188a)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **188a** as a white solid (131 mg, 86 % yield, Mp. 105-106 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.11-8.07 (2H, m), 8.01-7.98 (2H, m), 7.77-7.73 (2H, m), 7.53 (1H, s), 7.48-7.45 (3H, m), 2.59 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 196.9 (quat), 161.9 (quat), 150.1 (quat), 136.3 (quat), 131.9 (quat), 130.62 (CH), 129.0 (CH), 128.8 (CH), 127.0 (quat), 126.4

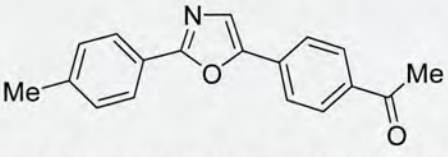
(CH), 125.5 (CH), 123.9 (CH), 26.5 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{17}H_{13}NO_2$ 263.0941, found 263.0950.

1-{4-[2-(4-Methoxy-phenyl)oxazol-5-yl]-phenyl}-ethanone (188c)



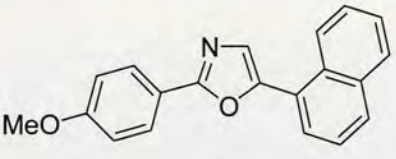
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **188c** as a off-white solid (151 mg, 89 % yield, Mp. 148-150 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.04-7.80 (4H, m), 7.76-7.72 (2H, m), 7.51 (1H, s), 6.99-6.96 (2H, m), 3.86 (3H, s), 2.60 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 197.1 (quat), 162.1 (quat), 161.6 (quat), 149.6 (quat), 136.2 (quat), 132.1 (quat), 129.0 (CH), 128.1 (CH), 125.4 (CH), 123.7 (CH), 119.8 (quat), 114.3 (CH), 55.4 (CH_3), 26.5 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{18}H_{15}NO_3$ 293.1046, found 293.1044.

1-[4-(2-*p*-Tolyl-oxazol-5-yl)-phenyl]-ethanone (188b)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **188b** as a white solid (149 mg, 93 % yield, Mp. 132-134 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.87-7.82 (4H, m), 7.62-7.59 (2H, d, *J*= 8.5 Hz), 7.38 (1H, s), 7.13 (2H, d, *J*= 8.0 Hz), 2.45 (3H, s), 2.26 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 197.0 (quat), 162.2 (quat), 149.8 (quat), 141.1 (quat), 136.2 (quat), 132.1 (quat), 129.5 (CH), 129.0 (CH), 126.4 (CH), 125.5 (CH), 124.3 (quat), 123.8 (CH), 26.5 (CH_3), 21.5 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{18}H_{15}NO_2$ 277.1097, found 277.1095.

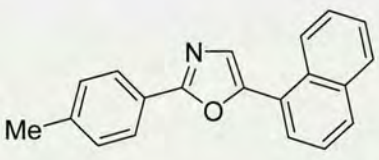
2-(4-Methoxy-phenyl)-5-naphthalen-1-yl-oxazole (189c)



Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **189c** as a white

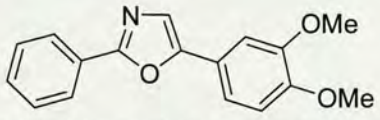
solid (132 mg, 76 % yield, Mp. 72-74 °C); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.37 (1H, m), 8.12-8.08 (2H, m), 7.92-7.81 (3H, m), 7.59-7.51 (4H, m), 7.04-7.00 (2H, m), 3.89 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.6 (quat), 161.4 (quat), 149.9 (quat), 133.9 (quat), 130.1 (quat), 129.3 (CH), 128.7 (CH), 128.0 (CH), 127.0 (CH), 126.5 (CH), 126.2 (2x CH), 125.5 (quat), 125.3 (CH), 124.9 (CH), 120.2 (quat), 114.3 (CH), 55.3 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{20}H_{15}NO_2$ 301.1097, found 301.1092.

5-Naphthalen-1-yl-2-*p*-tolyl-oxazole (189b)



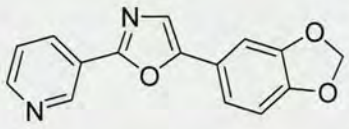
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **189b** as a white solid (133 mg, 81 % yield, Mp. 114-116 °C). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.38 (1H, m), 8.09-8.05 (2H, m), 7.94-7.82 (3H, m), 7.63-7.52 (4H, m), 7.34-7.30 (2H, m); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.7 (quat), 150.1 (quat), 140.6 (quat), 133.9 (quat), 130.1 (quat), 129.5 (CH), 129.4 (CH), 128.7 (CH), 127.0 (CH), 126.7 (CH), 126.3 (CH), 126.2 (CH), 125.4 (quat), 125.3 (CH), 124.9 (CH), 124.8 (quat), 21.5 (CH_3); **HRMS** (EI) *m/z* calcd for $C_{20}H_{15}NO$ 285.1148, found 285.1144.

Balsoxin (145)



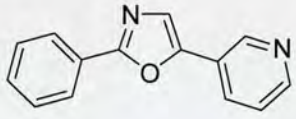
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **145** as a white solid (136 mg, 84 % yield) with identical spectral data to that previously reported: **^{1}H NMR** (250 MHz, $CHCl_3$) δ 8.11-8.07 (2H, m), 7.50-7.44 (3H, m), 7.33 (1H, s), 7.30 (1H, dd, *J*= 2.00Hz, 8.4Hz), 7.19 (1H, d, *J*= 2.0Hz), 6.93 (1H, d, *J*= 8.4Hz), 3.90 (3H, CH_3), 3.85 (3H, CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 160.5 (quat), 151.2 (quat), 149.4 (quat), 149.3 (quat), 130.1 (CH), 128.7 (CH), 127.5 (quat), 126.1 (CH), 122.2 (CH), 121.0 (quat), 117.2 (CH), 111.4 (CH), 107.4 (CH), 56.0 (CH_3), 55.9 (CH_3); **Mp**. 149-150°C; **HRMS** (EI) *m/z* calcd for $C_{17}H_{15}NO_3$ 281.1046, found 281.1046.

Texaline (36)



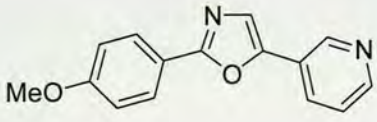
Prepared according to the general procedure. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **36** as a white solid (114 mg, 74 % yield) with identical spectral data and melting point to that previously reported. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 9.29 (1H, d, *J*= 1.5Hz), 8.66 (1H, dd, *J*= 1.7Hz, 4.9Hz), 8.30 (1H, m), 7.38 (1H, dd, *J*= 4.9Hz, 8.0Hz), 7.31 (1H, s), 7.21 (1H, dd, *J*= 1.8Hz, 8.0Hz), 7.14 (1H, d, *J*= 1.7Hz), 6.90 (1H, d, *J*= 8.3Hz), 6.00 (2H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 158.12 (quat), 151.83 (quat), 150.75, 148.23 (quat), 148.14 (quat), 147.40 (CH), 133.12 (CH), 123.63 (quat), 123.49 (CH), 122.47 (CH), 121.68 (quat), 118.53 (CH), 108.85 (CH), 104.82 (CH), 101.42 (CH_2); **HRMS** (EI) *m/z* calcd for $C_{15}H_{10}N_2O_3$ 266.0685, found 266.0684. **Mp**. 166-168°C.

3-(2-Phenyl-oxazol-5-yl)-pyridine (190a)



Prepared according to the general procedure. Purification by flash chromatography (silica, EtOAc 100 %) gave the coupled product **190a** as a white solid (42 mg, 36 % yield); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.99 (1H, dd, *J*= 0.77Hz, 2.3 Hz), 8.57 (1H, dd, *J*= 1.6Hz, 4.8 Hz), 8.12-8.08 (2H, m), 7.98 (1H, ddd, *J*= 1.7Hz, 2.2Hz, 8.0 Hz), 7.52-7.47 (4H, m), 7.35 (1H, ddd, *J*= 0.8Hz, 4.9Hz, 8.0 Hz); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 161.9 (quat), 149.3 (CH), 148.4 (quat), 145.6 (CH), 131.1 (CH), 130.6 (CH), 128.8 (CH), 127.0 (quat), 126.4 (CH), 124.7 (CH), 124.3 (quat), 123.6 (CH); **Mp**. 153-156°C; **HRMS** (EI) *m/z* calcd for $C_{14}H_{10}N_2O$ 222.0793, found 222.0791.

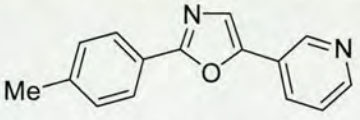
3-[2-(4-Methoxy-phenyl)-oxazol-5-yl]-pyridine (190c)



Prepared according to the general procedure. Purification by flash chromatography (silica, 1:1 hexane / ethyl acetate) gave the coupled product **190c** as a white solid (44 mg, 30 % yield); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.98 (1H, s), 8.57-8.55 (2H, m), 8.08-8.03 (2H, m), 7.96 (1H, m), 7.49 (1H, s) 7.39-7.34 (1H, m),

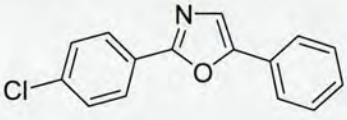
7.02-6.98 (2H, m), 3.88 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.1 (quat), 161.6 (CH), 149.0 (quat), 147.8 (quat), 145.4 (CH), 131.0 (CH), 128.1 (CH), 124.6 (CH), 123.6 (quat), 119.8 (quat), 114.3 (CH), 55.4 (CH_3); **Mp**. 160-161°C; **HRMS** (EI) *m/z* calcd for $C_{15}H_{12}N_2O_2$ 252.0895, found 252.0895.

3-(2-*p*-Tolyl-oxazol-5-yl)-pyridine (190b)



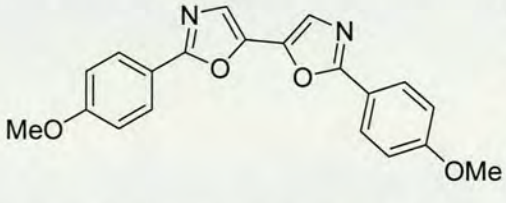
Prepared according to the general procedure. Purification by flash chromatography (silica, 1:1 hexane / ethyl acetate) gave the coupled product **190b** as a white solid (45 mg, 33 % yield); **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.98 (1H, s), 8.57 (1H, s), 8.01-7.95 (3H, m), 7.51 (1H, s), 7.37-7.26 (2H, m), 2.42 (3H, s); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.2 (quat), 149.1 (CH), 148.1 (quat), 145.5 (CH), 141.1 (quat), 131.1 (CH), 129.6 (CH), 126.4 (CH), 124.6 (CH), 124.4 (quat), 123.6 (quat), 21.5 (CH_3); **Mp**. 144-148 °C; **HRMS** (EI) *m/z* calcd for $C_{15}H_{12}N_2O$ 236.0950, found 236.0950.

2-(4-Chloro-phenyl)-5-phenyloxazole (212)



Prepared according to the general procedure for the direct arylation on the 5-position. Purification by flash chromatography (silica, DCM 100 %) gave the coupled product **212** as an off-white solid (105 mg, 71 % yield) with identical spectral data to that previously reported.[152] **^{1}H NMR** (250 MHz, $CDCl_3$) 8.04-8.01 (2H, m), 7.72-7.69 (2H, m), 7.48-7.41 (6H, m); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 160.1 (quat), 151.5 (quat), 136.3 (quat), 129.1 (CH), 129.0 (CH), 128.6 (CH), 127.8 (quat), 127.5 (CH), 125.9 (quat), 124.2 (CH), 123.5 (CH).

2-(4-Methoxyphenyl)-5-(2-(4-methoxyphenyl)oxazole-5-yl)oxazole (192)



Prepared according to the genearal procedure for the direct arylation on the 5-position. Purification by flash chromatography (silica, DCM 100%) gave the homocoupled product in 28% yield. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.95

(4H, d, J= 8.6Hz), 7.12 (2H, s), 6.94 (4H, d, J= 8.6Hz), 3.86 (6H, s). **^{13}C NMR** (63 MHz, $CDCl_3$) δ 162.1 (quat), 161.3 (quat), 138.0 (quat), 128.2 (quat), 128.0 (CH), 120.4 (CH), 114.2 (CH), 55.4 (CH_3). **Mp**. Not available. **HRMS**: Not available.

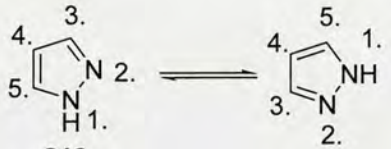
Chapter 2.

Direct Arylations of 2*H*-Indazoles

2.1. Introduction

2.1.1 Pyrazole and Indazole Numbering and Tautomerism

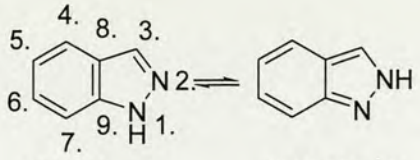
Pyrazole is an aromatic 5-membered heterocyclic ring with two nitrogens directly next to each other. Following IUPAC rules for heterocyclic structures such as this 1,2-diazole, the first nitrogen is given the number one position, the second nitrogen adjacent to the first one is given the number two and the following carbons are then numbered in an increasing order from three to five. Tautomerism plays an important role in the unsubstituted pyrazole core structure. The nitrogen which is bearing the hydrogen is always referred to as the first nitrogen.[153,154] This is of particular interest when considering the reactivity of the carbon atoms around the ring and will be discussed in detail later in this thesis.



213

Figure 14. Numbering and tautomerism of the pyrazole parent heterocycle.

Indazole, much like pyrazole exists in different tautomeric forms as shown below. The indazole building block is aromatic in its nature and contains a 5-membered pyrazole fragment which is substituted on two of the three carbons. Indazoles can exist as 1*H*-indazoles or 2*H*-indazoles. The more stable tautomer, when nitrogen is unsubstituted, is the 1*H*-indazole. The numbering of indazoles, much different than the numbering of pyrazoles, does not change depending on the tautomer. Commencing with the heteroatom closest to the benzene moiety (N1) the ring is then numbered following IUPAC rules with nitrogen two being (N2) and the sole unsubstituted carbon atom of the 5-membered ring becoming (C3). Spectroscopically all the carbons and hydrogens (NH is rapidly exchanged) of these two structures lie within the aromatic regions of the ^{1}H and ^{13}C NMR spectra, further underlining the aromatic nature of these compounds.[153,154]



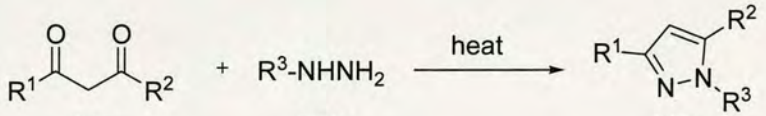
1H-Indazole **214a** 2H-Indazole **214b**

Figure 15. Numbering and tautomerism of indazole.

Pyrazole and indazole are planar compounds with a conjugated π-electron sextet in the cyclic system. The two electrons on the tertiary nitrogen are available for donation and give rise to the Lewis basicity while the lone pair of the NH nitrogen is involved in the π-electron system.[153,154]

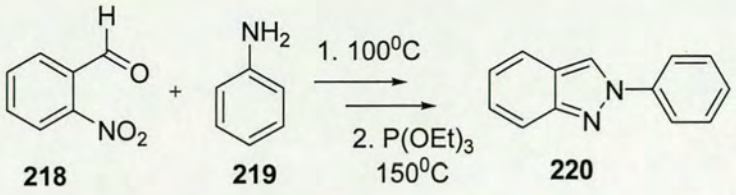
2.1.2 Synthesis of Pyrazoles and Indazoles

Both the synthesis of pyrazoles and indazoles are generally performed via a classical condensation reaction. Pyrazoles are widely generated via a condensation of a 1,3-dicarbonyl compound with a hydrazine derivative while indazoles are preferably synthesised via a condensation of aniline or aniline-analogues with the corresponding 2-nitro-benzaldehyde. Following the Schiffbase formation the imine is then reacted with triethylphosphite to give the 2*H*-substituted indazole.[154]



215 **216** **217**

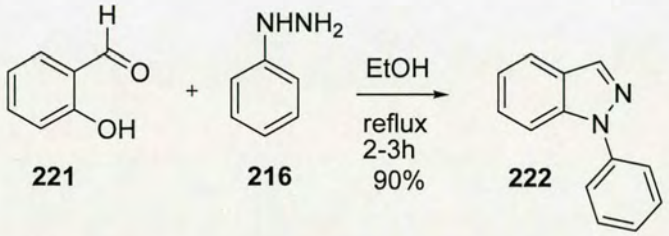
Scheme 67. Synthesis of substituted pyrazoles using 1,3-dicarbonyl compounds.[154]



218 219 220

Scheme 68. Two-step synthesis of 2-phenyl-2*H*-indazole.[154]

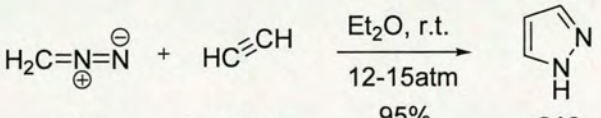
The most popular synthetic approach to 1*H*-substituted indazoles is the condensation of 2-hydroxy-benzaldehydes with phenyl hydrazines under refluxing conditions in EtOH.



221 216 222

Scheme 69. Synthesis of 1-Ph-1*H*-indazole via a condensation reaction.

This method is highly effective for the generation of 1-phenyl-1*H*-indazole and its analogues. Reaction times are as short as two hours.[154,155] Another synthesis of the pyrazole heterocycle is described below (Scheme 70). Using a positive pressure of ethyne and diazomethane, this 1,3-dipolar cycloaddition yields the parent pyrazole heterocycle without any substituents in excellent yields.[154]



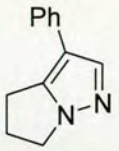
223 224 213

Scheme 70. 1,3-dipolar cycloaddition using ethyne to generate unsubstituted pyrazole.[154]

2.1.3 Pyrazoles and Indazoles in Natural Products

Pyrazoles and indazoles, very much like oxazoles belong to the family of π-excessive heterocycles. Both heterocycles are rather uncommon in nature. To date, only one

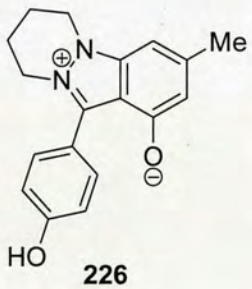
family of natural products containing a pyrazole and only three natural products containing an indazole core are known.[156,157] The alkaloid family of withasomnines has been reported.[156] Withasomnine (Figure 16, **225**) has been isolated from the roots of *Withania somnifer (Solanaceae), Newbouldia laevis*, the shrub *Elytraria acaulis*, and most recently from the stem bark of *Discopodium penninervium*.[158-160] Withasomnine displays both CNS and circulatory system depressant properties as well as being a mild analgesic.



225

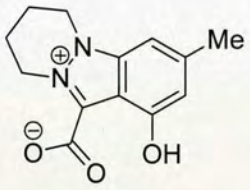
Figure 16. Withasomine, a rare pyrazole based natural product.[156]

Nigellidine and nigellicine, both indazole based natural products have been isolated from *Nigella sativa* seeds, which are used for their carminative, stimulatory as well as diaphoretic properties.[161]



226

Nigellidine



227

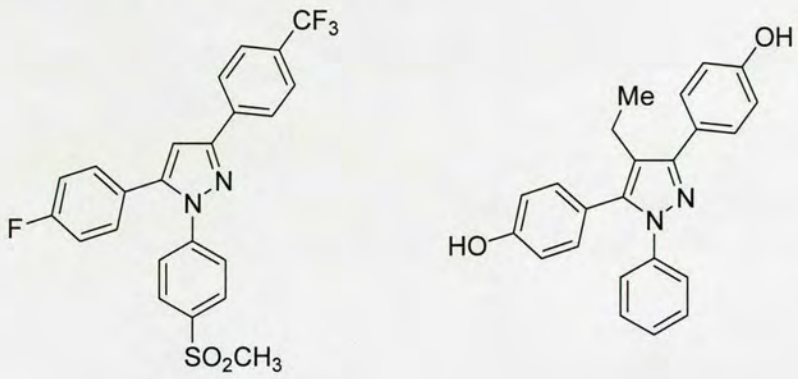
Nigellicine

Figure 17. Two indazole-containing natural products.

2.1.4 Pyrazoles and Indazoles in Medicinal Chemistry

Both indazoles and pyrazoles have found broad application in the pharmaceutical industry. Pyrazoles in particular have been very successful candidates in the drug

development process. Vioxx as well as Celebrex, both COX-II inhibitors have been hailed as potential new blockbuster drugs.[162,163]

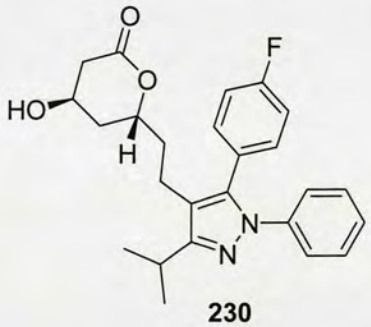


228
Celebrex
(anti-inflammatory)

229
RBA
(anti-cancer)

Figure 18. The pyrazole building-block in medicinal compounds.

However, both Celebrex and Vioxx have been withdrawn from the market on a temporary basis due to side-effects (cardiac arrest). Both of these drugs in addition to several others such as pyrazole mevalonolactone (Figure 19, **230**) and the anti-cancer drug RBA (Figure 18, **229**) have the pyrazole fragment as a common feature. It should be noted that most pyrazole based pharmaceuticals present with a phenyl group (substituted or unsubstituted) on the nitrogen atom.[162,163]



230

Pyrazole mevalonolactone
(cholesterol lowering)

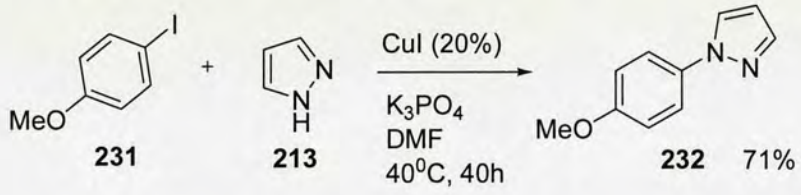
Figure 19. Structure of pyrazole mevalonolactone.

Indazoles, also known as benzopyrazoles have so far not been marketed as drugs, they appear however in the patent literature quite commonly and are associated with biological activities towards many drug targets, particularly towards cardiovascular diseases.[164]

2.2 Pyrazole / Indazole Arylations to Date

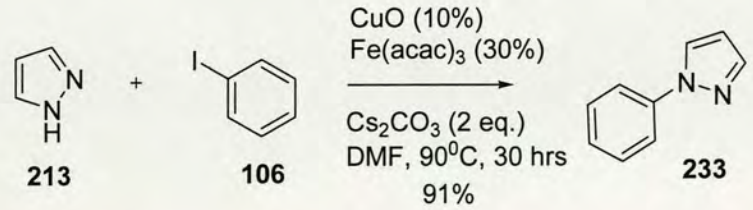
2.2.1 N-Arylations

The *N*-arylation of pyrazole is a well documented transformation in the literature. Generally this type of reaction is catalysed by metals such as copper or cobalt (Scheme 71). In 2009, You and co-workers reported the ligand-free Cu-catalysed *N*-arylation of pyrazoles. It is noteworthy that these conditions are highly functional group tolerant, given that the reactions work well at temperatures as low as 40 °C.[165]



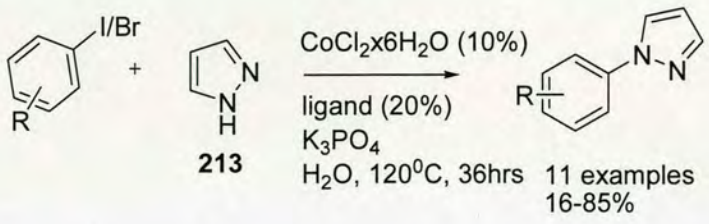
Scheme 71. Cu-catalysed N-arylation of pyrazole using aryliodides under Jeffrey conditions.[165]

Other strategies to generate *N*-arylated pyrazoles include the iron / copper co-catalysed reaction of arylbromides or aryliodides with pyrazole.[166]



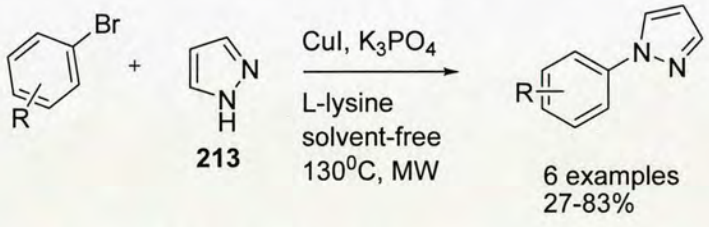
Scheme 72. Efficient iron / copper co-catalysed arylation of pyrazole.[166]

Further, Teo and Chua developed an interesting *N*-arylation in which the components are reacted in water. The combination of $CoCl_2\ xH_2O$ and the effective ligand N,N-dimethylethylenediamine allowed the authors to generate a small library of phenyl-substituted pyrazoles.[167]



Scheme 73. Co-catalysed *N*-arylation of pyrazole using arylhalides. (ligand: dmeda)[167]

An additional example, this time showing the strength of microwave technology, was described by Chow *et al.* in 2009. The authors developed an arylation method using amino-acids in addition to the typical copper catalyst needed for such transformations. Highlights of this preparation are the lack of solvent as well as the introduction of microwave heating to the arylation of pyrazoles.[168]

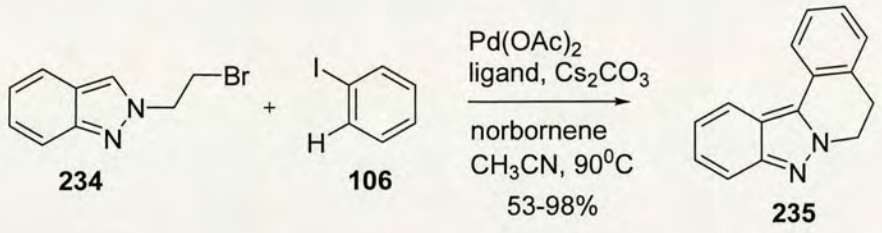


Scheme 74. MW-assisted Cu-catalysed *N*-arylation of pyrazoles using arylbromides.[168]

2.2.2 C-Arylations

Arylation of pyrazoles and indazoles are well known in the literature.[169-171] Pyrazoles for example have been arylated using many traditional cross coupling methods such as the Stille, Negishi or Suzuki reaction. A Scifinder search for the words 'direct arylation' as well as 'indazole' only identified four publications. One of the

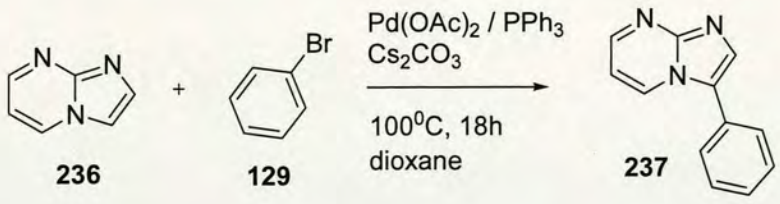
publications is a patent regarding the biological activity of indazoles for the treatment of diseases associated with protein kinases, showing the medical importance of these compounds. The only other relevant article from this query is a publication from Laleu and Lautens.[172] The paper describes the one-pot palladium catalysed alkylation / direct arylation of 2*H*-indazoles and triazoles (1,2,3- as well as 1,2,4-triazoles). Scheme 75 highlights the reaction conditions for this reported transformation. It should be noted that the authors added the indazole / triazole starting materials via a syringe pump over 20 hrs to avoid catalyst poisoning by the nitrogen atoms of the heterocycle. This important problem will be discussed in detail in the later stages of this thesis.



234 106 235

Scheme 75. One-pot alkylation / direct arylation of 2-alkyl-indazoles.[172]

Two further examples of direct arylations on similar heterocyclic systems should be highlighted in this section. Gevorgyan's palladium catalysed arylation of indolizines as described in chapter 1 and Li's palladium catalysed regio-selective arylation of imidazo[1,2-a]pyrimidine (**236**) are clearly closely related and of interest (Scheme 76).



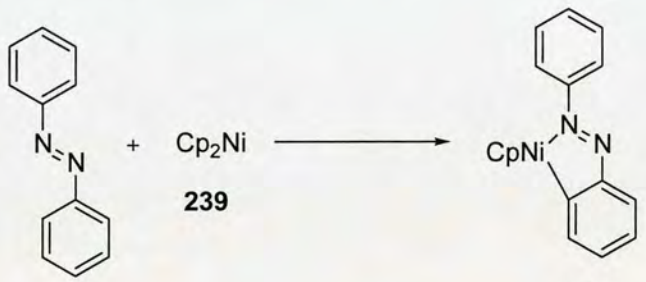
236 129 237

96%

Scheme 76. Li and co-workers' Pd-catalysed direct arylation of imidazo[1,2-a]pyrimidine.[173]

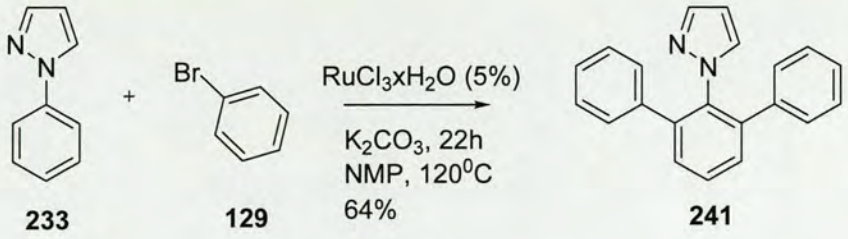
As proposed in Gevorgyan's work, Li and colleagues support a mechanism based on the electrophilic substitution for these type of molecules. The authors argue that the substitution occurs on the imidazole-type part of the compound as it is π-excessive with the Western part of the molecule being π-deficient and more likely to be attacked by a nucleophile in the positions directly adjacent to the nitrogens, but not reactive towards electrophilic substitution.[173]

The direct arylation of pyrazoles is as uncommon in the literature as the direct arylation of indazoles. Firstly, one has to clearly distinguish between the TM-catalysed direct arylation of pyrazole itself, or the TM-catalysed direct arylation of a substituent (such as a phenyl group), which is coupled to one of the nitrogens of the pyrazole (also referred to as '*ortho*' arylation or '*ortho*' direct arylation). The latter is a direct arylation of pyrazole based on the directing effects of the nitrogen and is generally catalysed by ruthenium as highlighted by much of Ackermann's work.[174] The concept of using a directing group to control regioselectivity of the subsequent transition-metal insertion into a C-H bond was initially reported by Dubeck and Kleinman over four decades ago.[175]



238 **240**

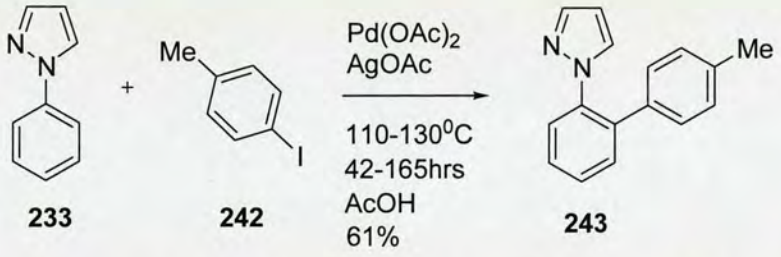
Scheme 77. First regioselective directing group controlled metallation.



233 129 241

Scheme 78. Ackermann's Ru-catalysed di-*ortho* arylation of phenyl pyrazole.[174]

The only palladium catalysed mono-*ortho* arylation examples to date were published in 2005 by Daugulis and co-workers.[176] The authors described a rather harsh method to arylate phenyl-pyrazole using 3 - 5 eq. of aryliodides, 1 - 3 eq. of a silver base as well as 5 % catalyst. Reaction times ranged from 42 - 165 hrs (!) and temperatures were in the range of 110 - 130 °C.

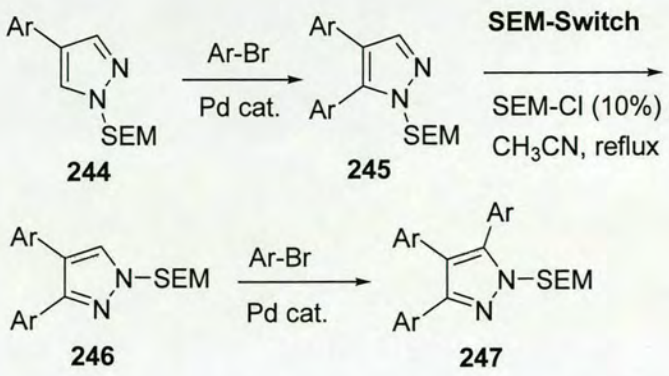


233 242 243

Scheme 79. Mono-*ortho* arylation of phenyl-pyrazole using Pd-catalyst.[176]

Ortho arylation / directing group arylation of heterocycles and its substituents is a highly interesting and much researched field (see thesis of Dr. Turner, Greaney group, 2008), however we will not discuss this area in detail in this document. Recent examples of directing group arylations of heterocycles such as pyridine, oxazoline, imidazole etc. exist in the literature.[177-179]

An excellent example showing the power of direct arylation methodology work was recently described by Sames *et al.* This article was published while research on this topic was ongoing in our laboratories. Sames described the 5-arylation of SEM-protected pyrazoles using arylbromides for this sp^2-coupling.[180]



Scheme 80. Multiple direct arylations on SEM-protected pyrazole.[180]

The above described 5-arylation of pyrazoles represents the first direct arylation of any pyrazole in the literature. A highly exciting SEM-switch was used to transform the unreactive 3-position into a 5-position. This switch allows for a second direct arylation. It is known from empirical data (reported in the above paper) that the 5-position of *N*-substituted pyrazole is most acidic, the 4-position is most nucleophilic and the 3-position is mostly unreactive as it is neither electron rich nor as acidic as the 5-position.[180]

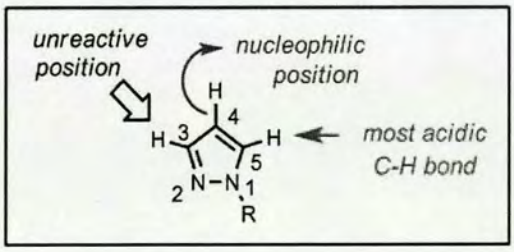


Figure 20. Reactivity of *N*-substituted pyrazole.[180]

The SEM-switch allows the previously unreactive 3-position to become a 5-position and therefore react in the same way as the initial step of the above sequence. It should be noted that the authors of the publication above have not commented or investigated any *N*-phenyl substituted pyrazoles.

The only further example of a pyrazole direct arylation was also published by Sames and coworkers.[181] This report in 2003 described the reaction of the parent pyrazole heterocycle with iodobenzene under Grignard conditions in which the 3-position of pyrazole could be arylated using palladium catalysis. This report however was again retracted by Sames on June 21st, 2006.

2.3 Aims of Project

The importance of pyrazoles and related structures in medicinal chemistry and drug discovery is undisputed.[162-164] The goal of this project was to identify mild and clean reaction conditions for the direct transformation of the parent heterocycles into late-stage-diversified analogues. Traditionally, many of the pyrazole and indazole structures have to be diversified at an early stage, sometimes prior to a low-yielding condensation reaction. Recent developments of TM-catalysed cross couplings have allowed a late stage diversification. However, both the parent heterocycle as well as the arylhalide or pseudohalide have to be functionalised prior to the coupling reaction as described in the first chapter of this thesis. We seek to develop a method to utilise our previously successful on water chemistry to directly arylate pyrazoles and indazoles in a mild, selective and efficient fashion.

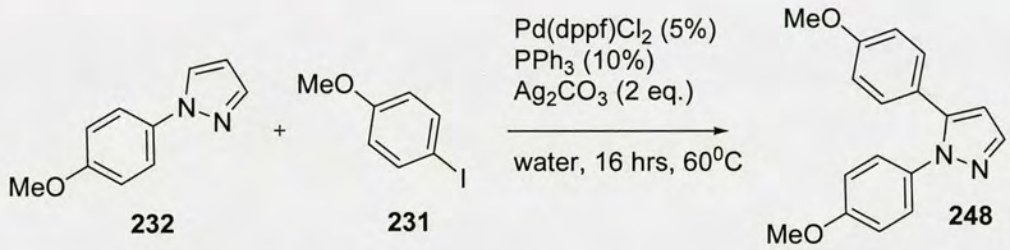
2.4 Results and Discussion

2.4.1 Preparation of Starting Materials

Starting materials for the screening of the on water conditions were synthesised using the previously described (*vide supra*) methods for the generation of *N*-aryl-pyrazoles. Best yields were obtained when utilising the copper / iron co-catalysed conditions described in scheme 72.[166]

2.4.2 Initial Screening and Optimisation

Initial trial reactions on the on water direct arylation of pyrazoles were performed by Clemmentine Stubbs, supervised by Stephan Ohnmacht during a five-month B.Sc. thesis at the University of Edinburgh. Initial screening of the previously published on water conditions as described by Turner *et al.* (2007) and Ohnmacht *et. al.* (2008) yielded several arylated pyrazoles in yields of up to 30 %, isolated.[122,182] Following the departure of C.Stubbs, I was asked to investigate these reactions further.



Scheme 81. Discovery of reactivity of pyrazole towards on water direct arylation.

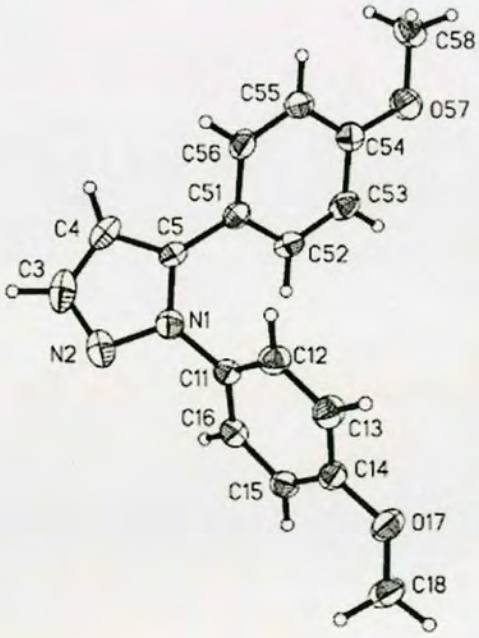
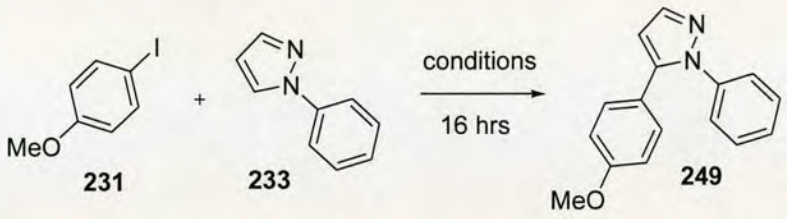


Figure 21. X-ray crystal structure of 5-arylated pyrazole **248**.

Having supervised the on water attempts to arylate pyrazole with no organic solvents, while also growing crystals to obtain a crystal structure to determine the regioselectivity of these reactions, it was decided to investigate the use of organic solvents for such a transformation. Table 7 shows a general solvent screen.

Table 7. Screening of organic solvents.



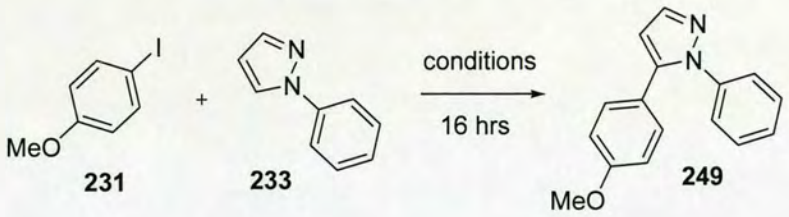
	Temp.(°C)	*Base(2eq.)*	*Solvent*	*Pd-source(5%)*	Ligand	*Product*
i.	120	Ag_2CO_3	NMP	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
ii.	120	Ag_2CO_3	Dioxane	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
iii.	120	Ag_2CO_3	THF	$Pd(dppf)Cl_2$	PPh_3	No conv.
iv.	120	Ag_2CO_3	Benzene	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
v.	120	Ag_2CO_3	DMF	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
vi.	120	Ag_2CO_3	o-Xylene	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
vii.	120	Ag_2CO_3	MeCN	$Pd(dppf)Cl_2$	PPh_3	No conv.
viii.	120	Ag_2CO_3	DMSO	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
ix.	60	Ag_2CO_3	Neat	$Pd(dppf)Cl_2$	PPh_3	Formed[a)]
x.	120	Ag_2CO_3	Ethyldiglycol	$Pd(dppf)Cl_2$	PPh_3	No conv.

a) Product is formed but conversion is lower than with the 'on water' reaction.

Entry *i.* to *x.* (Table 7) provide an overview over the success of organic solvents for the 5-arylation of phenyl-pyrazole (**233**). It can be seen that none of the solvents of choice have performed better than the on water conditions previously examined. Increased temperatures and complete solubility of the starting materials (not the silver source) drastically increased the occurrence of side-reactions such as homo-coupling of the halide. None of the above reactions occurred in a clean fashion and therefore showed no advantage over the already existent on water reactions. No

further investigations into the use of organic solvents were initiated. Focus was directed towards the optimisation of our own on water methodology.

Table 8. Buchwald ligand screen using $Pd(OAc)_2$ catalyst.



	Cat. %	*Base*	*Solv.*	*Pd-source*	Ligand	*Product*
i.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	1	No conv.
ii.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	2	No conv.
iii.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	3	No conv.
iv.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	4	No conv.
v.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	5	No conv.
vi.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	6	No conv.
vii.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	7	No conv.
viii.	5	Ag_2CO_3	H_2O	$Pd(OAc)_2$	8	No conv.

Early attempts to optimise our conditions focused on a ligand screen. Novartis UK (Dr. A.J. Culshaw) kindly provided our laboratories with a Buchwald ligand screen kit as sold by Aldrich UK. Eight sterically demanding and electronically diverse Buchwald ligands (Table 8 and Figure 22) were screened using phenyl-pyrazole (**233**) and the previously moderately successful 4-iodo-anisole (**231**).

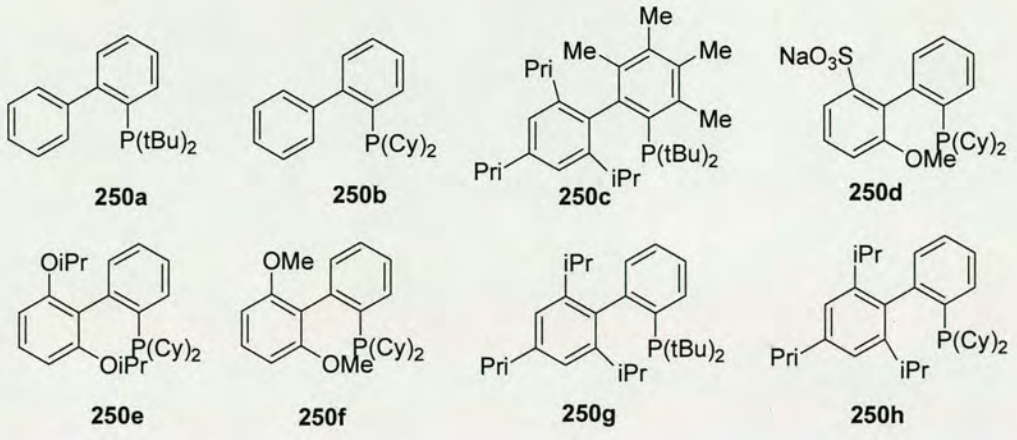
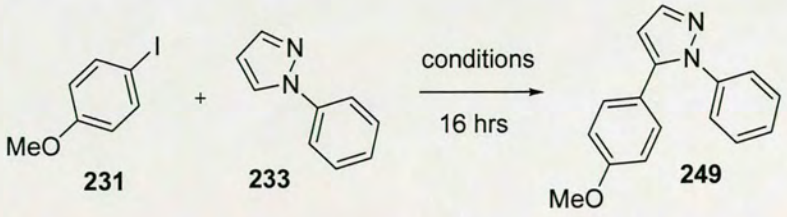


Figure 22. Selection of screened Buchwald ligands.

$Pd(OAc)_2$ was the catalyst of choice as most of the Buchwald ligand literature uses either $PdCl_2$ or $Pd(OAc)_2$, as the Pd^{II} source.[183] Unfortunately none of the ligands, including a test-reaction with PPh_3 as the ligand, promoted the formation of an arylated pyrazole product.

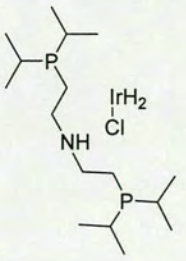
Before focusing our research efforts entirely into the strictly Pd-catalysed direct arylation, we decided to investigate other potential active transition metals such as Rh, Re, Ru and Ce. Table 9 shows the outcome of a detailed screening of available metal sources in the Greaney group. It is noteworthy that TM-sources B-E gave traces of the desired product on the LCMS. This has to be interpreted with caution as the same reaction, without any TM, also provides traces of product. Ag_2CO_3 is believed to be the reason for this small turnover. If the reaction is run without any silver source or with a substitute base such as K_2CO_3, it does not promote any product formation at all.

Table 9. TM-screening using 'on water' conditions.



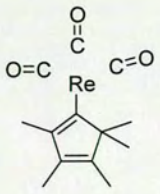
	Temp.(°C)	*Base(2eq.)*	*Solv.*	*TM-source(5%)*	Ligand	*Product*
i.	60	Ag_2CO_3	H_2O	A	PPh_3	No conv.
ii.	60	Ag_2CO_3	H_2O	B	PPh_3	Traces
iii.	60	Ag_2CO_3	H_2O	C	PPh_3	Traces
iv.	60	Ag_2CO_3	H_2O	D	PPh_3	Traces
v.	60	Ag_2CO_3	H_2O	E	PPh_3	Traces
vi.	60	Ag_2CO_3	H_2O	F	PPh_3	No conv.
vii.	60	Ag_2CO_3	H_2O	G (+ ligand 1)	PPh_3	No conv.
viii.	60	Ag_2CO_3	H_2O	H (+ ligand 2)	PPh_3	No conv.
ix.	60	Ag_2CO_3	H_2O	I	PPh_3	No conv.
x.	60	Ag_2CO_3	H_2O	K	PPh_3	No conv.
xi.	60	Ag_2CO_3	H_2O	L	PPh_3	No conv.

A = **251**, B = **252**, C = **253**, D = **254**, E = **255**, F = **256**, G = **257**, H = **258**, I = **259**, K = **260**, L = **261**.



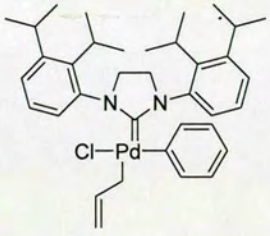
251

Chlorodihydrido[bis(2-di-i-propylphosphino -ethyl)amine]iridium(III)



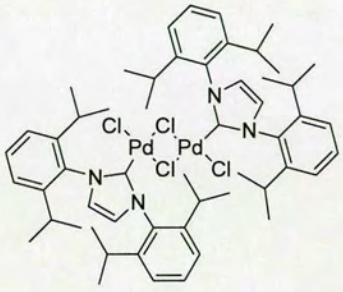
252

Pentamethyl cyclopentadienyl rhenium tricarbonyl



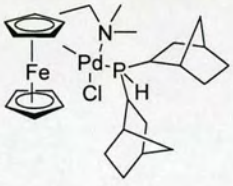
253

Chloro[(1,2,3-n)-3-phenyl-2-propenyl] [1,3-bis(2,6-di-i-propylphenyl)-4,5-dihydro imidazol-2-ylidine]palladium(II)



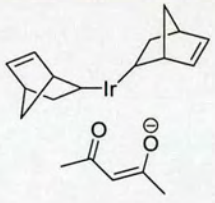
254

Dichloro(di-mu-chloro)bis[1,3-bis (2,6-di-i-propylphenyl) imidazole-2-ylidine dipalladium(II)



255

Chloro(di-2-norbornylphosphino) (2-dimethylaminomethyl ferrocen-1-yl palladium(II)



256

Tris-(norbornadiene)-acetylacetonato) iridium(III)

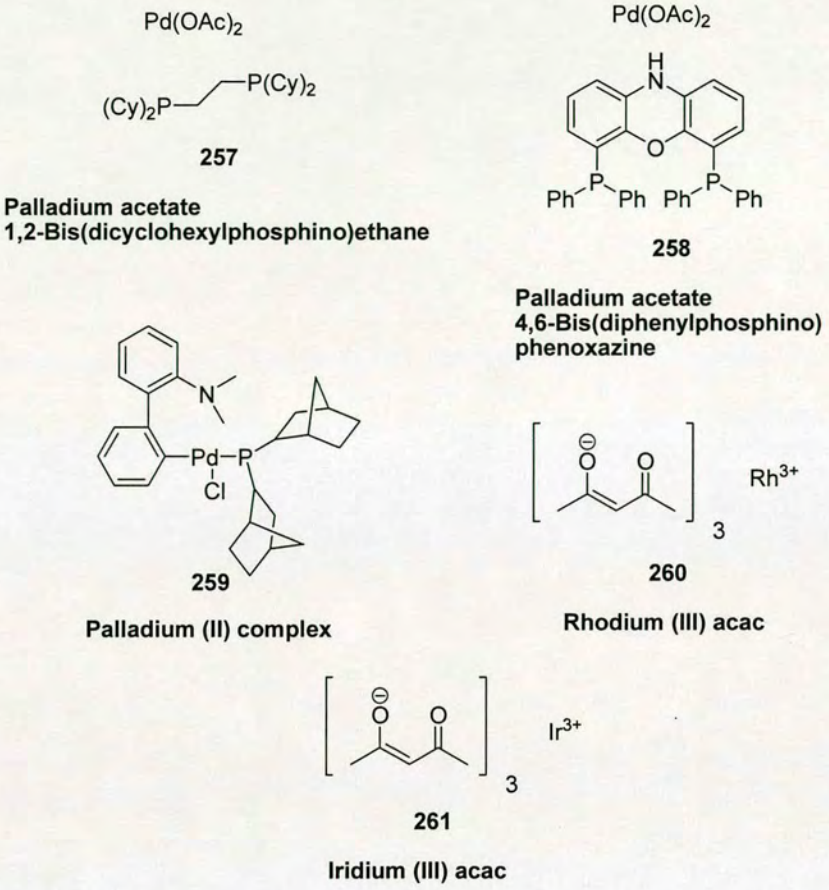
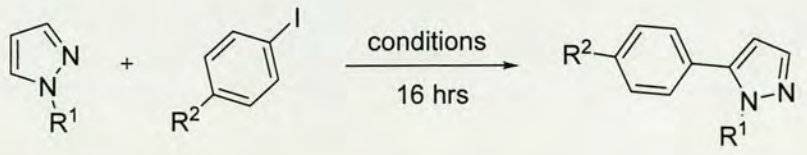


Figure 23. Structures of screened transition metals.

Following the unsuccessful screening of ligands (Table 8) and TM-catalysts (Table 9) the decision was made to thoroughly examine the use of other *N*-substituted pyrazoles while varying the arylhalide at the same time. Table 10 shows preliminary data using the standard conditions developed in the first chapter of this thesis with slight changes to the reaction temperature.

Table 10. Screening of a variety of *N*-substituted pyrazoles with differing halides.



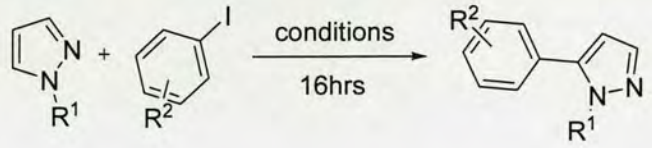
	Pyrazole	*Base*	*Halide*	*Pd-source(5%)*	*Temp.(°C)*	*Product*
i.	N-CH_3	Ag_2CO_3	*p*-Br	$Pd(dppf)Cl_2$	80	Traces
ii.	N-CH_3	Ag_2CO_3	*p* -OMe	$Pd(dppf)Cl_2$	80	Traces
iii.	N-(2-pyridyl)	Ag_2CO_3	*p* -OMe	$Pd(dppf)Cl_2$	60	Traces
iv.	N-(2-pyridyl)	Ag_2CO_3	*p*-Br	$Pd(dppf)Cl_2$	60	35%
v.	N-(2-pyridyl)	Ag_2CO_3	*p* -CO_2Et	$Pd(dppf)Cl_2$	80	No conv.
vi.	N-(2-pyridyl)	Ag_2CO_3	*p*-CN	$Pd(dppf)Cl_2$	80	Traces
vii.	N-(2-pyridyl)	Ag_2CO_3	*p*-OMe	$Pd(dppf)Cl_2$	60	Traces
viii.	N-Boc	Ag_2CO_3	*p*-OMe	$Pd(dppf)Cl_2$	60	No conv.
ix.	N-phenyl[a]	Ag_2CO_3	*p*-Br	$Pd(dppf)Cl_2$	60	No conv.
x.	N-phenyl[a]	Ag_2CO_3	*p*-OMe	$Pd(dppf)Cl_2$	60	No conv.
xi.	N-SEM	Ag_2CO_3	*p*-OMe	$Pd(dppf)Cl_2$	60	Traces
xii.	N-SEM	AgF	*p* -CO_2Et	$Pd(dppf)Cl_2$	60	Traces

[a] Arylhalide was added in excess (3 eq.).

Unsatisfactory results were obtained from this screen. None of the selected *N*-substituted pyrazoles were by any means better than the previously explored starting materials. None of the *N*-alkyl reactions worked to give an isolable yield. The only example showing promising conversions was the *N*-(2-pyridyl)-pyrazole when coupled with *p*-bromo-iodobenzene (Entry *iv.*). Still however, yields did not exceed the 30 - 35 % barrier. It should also be noted that if multiple equivalents of halide are used, the yields drastically drop. The reason for that is that the effective concentration and surface area of each of the reagents is decreased due to the existence of a larger amount of a single reactant (Entry x., Table 10). This phenomenon has been observed for many of the on water reactions discussed in this thesis.

A further, more detailed halide screening was initiated and provided an even more in depth view into the reactivity of these pyrazoles.

Table 11. Screening of eight diverse arylhalides.



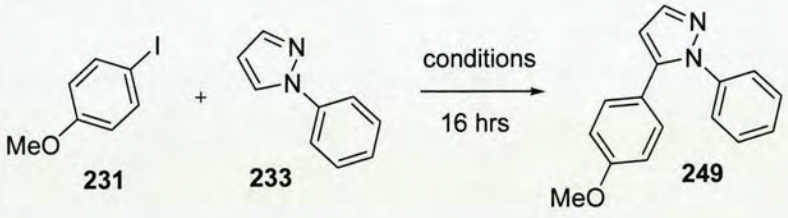
	Pyrazole	*Base*	*Halide*	*Pd-source(5%)*	*Temp.(°C)*	*Product*
i.	N-Ph	Ag_2CO_3	*m* -CF_3	$Pd(dppf)Cl_2$	60	Traces
ii.	N-Ph	Ag_2CO_3	*p* -CN	$Pd(dppf)Cl_2$	60	Traces
iii.	N-Ph	Ag_2CO_3	*p* -Me	$Pd(dppf)Cl_2$	60	Traces
iv.	N-Ph	Ag_2CO_3	*p* -CO_2Et	$Pd(dppf)Cl_2$	60	Traces
v.	N-Ph	Ag_2CO_3	*o* -Me	$Pd(dppf)Cl_2$	60	Traces
vi.	N-Ph	Ag_2CO_3	*p* -Cl	$Pd(dppf)Cl_2$	60	Traces
vii.	N-Ph	Ag_2CO_3	*m* -NO_2	$Pd(dppf)Cl_2$	60	Traces
viii.	N-Ph	Ag_2CO_3	*o* -Iodo-pyridyl	$Pd(dppf)Cl_2$	60	No conv.

Again, none of the reactions showed a good turnover using our catalytic system based on the $Pd(dppf)Cl_2$xDCM and PPh_3 combination. At this point poisoning of the catalyst by the pyrazole moiety was strongly considered and evidence supporting this issue was found in the literature.[184,185] It is commonly known that pyrazole have a high affinity for transition metals such as copper and palladium. In Lautens' review it states:[87] "While yields were lower than those of the analogous pyrrole systems, pyrazoles represent a challenging class of heterocycle, since the pyrazole nitrogen functionality may tightly bind to the catalyst, thereby acting as a catalyst poison." Several papers highlight and even describe specific syntheses of pyrazoles which act as strong ligands for these metals. The possibility of adding extra catalyst to our system was (e.g. after 6 h or 16 h) made more difficult by having water as our 'solvent'. Practical issues prevented any real further investigations as all of the starting materials were at the bottom of the vial, molten and not dispersed in the

water at all. Adding extra catalyst or ligands proved unhelpful as they did not submerge or mix with the already molten starting materials. Removal of the water, followed by addition of the solids and re-introduction of the removed water also did not improve the isolated yields of these transformations. Additionally, slow addition of the pyrazole building block was investigated but turned out to be of no use.

A final ligand screen, based on the limited success of the dppf (diphenylphosphino ferrocene) ligand was commenced. Ligands such as dppp (entry i.), dpph (entry ii.), 2,2-dipyridyl (entry iii.), dppe (entry iv.), dppb (entry v.) as well as dppm (entry vi.) all did not show any improvement over the original dppf-type conditions and were therefore not isolated. (Table 12). Interestingly, when dppf was added together with separate $PdCl_2$, (instead of the commercially available $Pd(dppf)Cl_2$) no measurable conversion occurred. Mixing and controlling the surface area of this heterogeneous mixture seem to be of paramount importance.

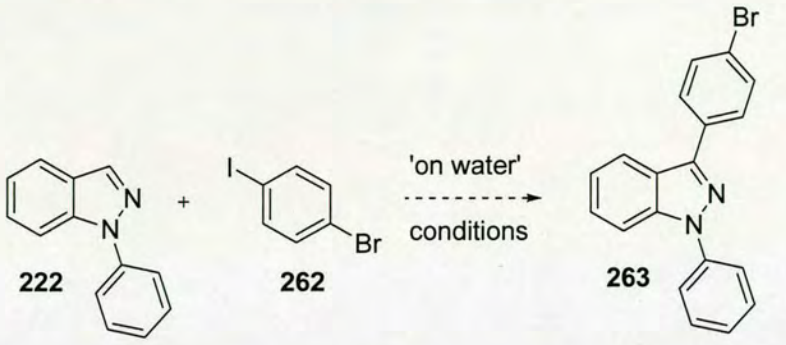
Table 12. Ligand screening using on water conditions.



	Cat. %	*Base (2Eq.)*	*Solv.*	*Pd-source*	Ligand	*Product*
i.	5	Ag_2CO_3	H_2O	$PdCl_2$	dppp	Formed[a)]
ii.	5	Ag_2CO_3	H_2O	$PdCl_2$	dpph	Formed[a)]
iii.	5	Ag_2CO_3	H_2O	$PdCl_2$	2,2-bipy	No conv.
iv.	5	Ag_2CO_3	H_2O	$PdCl_2$	dppe	Formed[a)]
v.	5	Ag_2CO_3	H_2O	$PdCl_2$	dppb	Formed[a)]
vi.	5	Ag_2CO_3	H_2O	$PdCl_2$	dppm	Formed[a)]

[a)] conversion less than original on water conditions (< 10%).

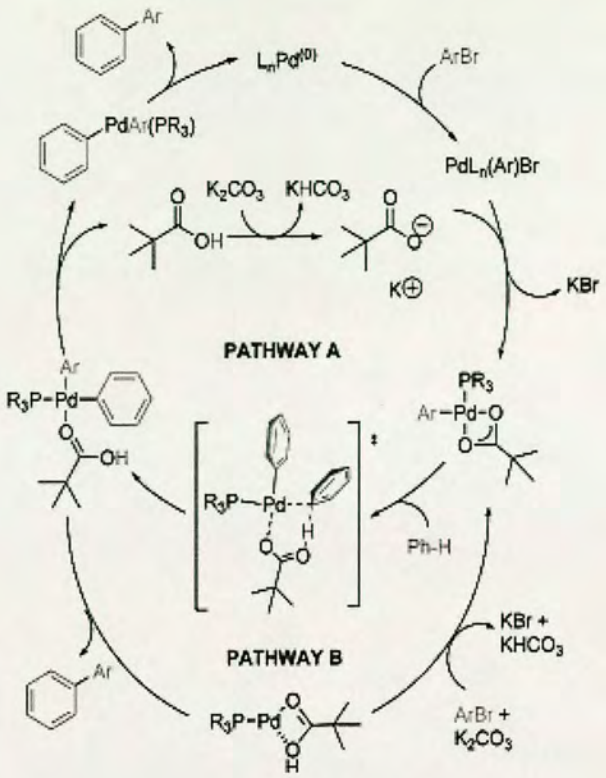
At this point of the project it seemed appropriate to explore other heterocyclic compounds closely related to pyrazoles. Indazole, as described earlier presented itself to be a worthy choice.



Scheme 82. Attempt to arylate 1-phenyl-1*H*-indazole.

The arylation of 1-Phenyl-1*H*-indazole (**222**) was investigated but quickly turned out to be as unsuccessful as the attempts to arylate pyrazole. 1-Phenyl-1*H*-indazole did not provide any product following TLC or LCMS analysis.

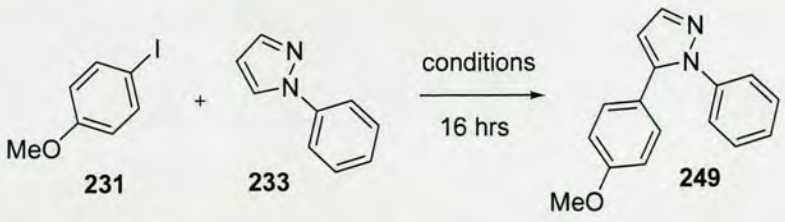
A further screening based on the pyrazole heterocycle was envisioned. A range of acids and bases were investigated as additives for the transformation below. The idea of a further catalytic additive was taken from the successful use of pivalic acid by Fagnou and co-workers.[100] The authors described the incorporation of catalytic pivalic acid as a proton shuttle for the arylation of benzene with bromobenzene. Scheme 83 highlights this exciting finding in more detail.



Scheme 83. Fagnou's pivalic acid proton shuttle mechanism.[100,101]

Given the success of this discovery we investigated the use of pivalic acid and other additives in our system. The 5-position of pyrazole is the most acidic position, therefore the potential of C-H bond cleaving by the pivalate anion seemed reasonable. However, we could not observe any increase in conversion or yields using this method. In fact, this additive (Table 13, entry *iv.*) turned out to be performing worse than the reactions without the pivalic acid. Other additives such as K_2CO_3, Cs_2CO_3 or Na_2CO_3 performed equally well as the reaction without additive (Entries *i., iii., v., vi., vii., viii.*) showing that an extra carbonate source is not detrimental to the system but in some cases increased the isolated yields by a few percent. NH_4Cl, LiCl, NaOH, Na_2HPO_4 and NaOAc on the other hand did not promote any turnovers and allowed for no products to be formed.

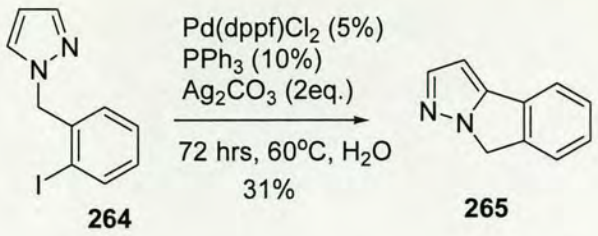
Table 13. Additive screening on water.



	Additive(eq.)	*Base(2eq.)*	*Time*	*TM-source(5%)*	*Ligand*	*Product*
i.	K_2CO_3 (2)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	38%[a]
ii.	K_2CO_3 (2)	-	72h	$Pd(dppf)Cl_2$	PPh_3	No conv.
iii.	K_2CO_3 (2)	Ag_2CO_3	72h	$Pd(dppf)Cl_2$	PPh_3	34%[a]
iv.	PivOH (0.3)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	Traces
v.	Cs_2CO_3(2)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	As *iii.*[b]
vi.	Na_2CO_3 (2)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	As *iii.*[b]
vii.	K_2CO_3 (1)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	As *iii.*[b]
viii.	K_2CO_3 (2)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$ (10%)	PPh_3	As *iii.*[b]
ix.	K_2CO_3 (2)	-	72h	$Pd(dppf)Cl_2$	PPh_3	No conv.
x.	NaOH (1)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	No conv.
xi.	NaOAc (1)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	No conv.
xii.	LiCl (1)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	No conv.
xiii.	Na_2HPO_4(1)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	No conv.
xiv.	NH_4Cl (1)	Ag_2CO_3	16h	$Pd(dppf)Cl_2$	PPh_3	No conv.

a)isolated yield after silica chromatography b)not isolated but same conv.

A further more detailed screening of conditions and reagents was attempted. Attempts to arylated the *N*-phenyl pyrazole heterocycle using water / organic solvent mixtures did not improve yields (Table 14, entry *ii.* and *iv.*). Additionally, the direct arylation was investigated in neat conditions, omitting the use of water or any other solvent. This transformation yielded the product using $Pd(dppb)Cl_2$, but the isolated yield acquired was lower than the previously obtained yields when water was used as the medium (Entry *i.*). Further the intramolecular direct arylation reaction was investigated. The starting material was formed using a known procedure in which pyrazole was reacted with 2-iodo-benzylbromide to form **264** (Scheme 84).[186]

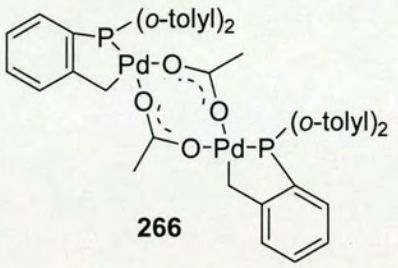


Scheme 84. Intramolecular direct arylation of *N*-benzyl substituted pyrazole.

The benzyl-substituted pyrazole **264** was reacted with base, catalyst, PPh_3 and stirred at 60 °C over the weekend (65 hrs). Compound **265** has not been synthesised previously. The only literature reference to this molecule is in a communication of Mori and his co-workers.[186] They describe the intramolecular reaction of the above substrate as an imidazole, not a pyrazole. Temperatures of 140 °C in combination with palladium catalysts are used to generate this imidazole analogue but the pyrazole intramolecular product was not successfully obtained (reported yield in Mori's paper = 0 %).[186] Further examples from the screening (Table 14) include the use of triphenylphosphine oxide instead of triphenylphosphine (Entry *xi.*). This reaction was performed to determine if triphenylphosphine indeed was necessary or if the phosphine during the time of the reaction actually gets oxidised and then becomes active towards the direct arylation. As expected, the use of triphenylphosphine oxide instead of triphenylphosphine did not yield any product.

Additionally, attempts were made to add different amounts of catalysts (and indeed PPh_3 as well) in a continuous manner to avoid poisoning of the catalyst (see Lautens' intramolecular arylation of indazole). This proved very difficult and all attempts 'on water' failed with isolated yields well below the previous amounts. (Entry *xv.*, *xviii.*, *xxiii.*) Even the use of DMF as a solvent instead of water did not help to generate a yield above 30%. (Entry *xii.*)

Several variations of catalyst loadings were also investigated – using 10 % catalyst loading (Entry *xiv.*) as well as attempting this transformation with a completely different catalytic system based on the recent success of the Hermann-Beller palladacycle (**266**), which becomes active at temperatures above 80°C while requiring toluene as the solvent and Cs_2CO_3 as the base of choice.(Entry *ix.*)[187-190]

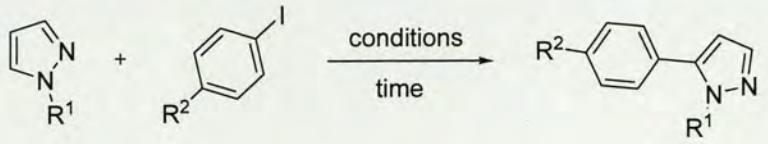


266

Figure 24. Structure of Hermann-Beller palladacycle.[190]

Both reactions did not produce exciting results with the Hermann-Beller system providing no products at all and the 10 % catalyst loading reaction (Entry *xiv.*) giving the same yields as the reactions with 5 % catalytic loading.

Table 14. Further screening of selected conditions.

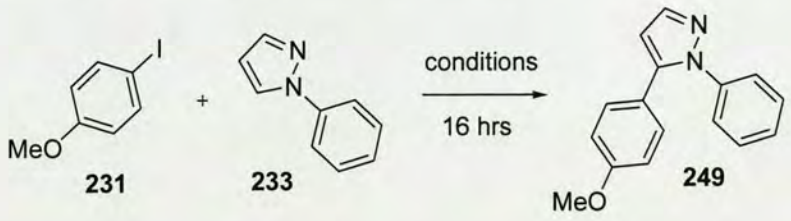


	Pyrazole	*Solvent*	*Halide(1.5eq.)*	*Pd-source(5%)*	*Temp.(°C)*	*Time(h)*	*Product*
i.	N-Ph	Neat	*p*-Br	$Pd(dppb)Cl_2$	60	16	25%
ii.	N-Ph	Tol:H_2O (4:1)	*p*-Br	$Pd(dppb)Cl_2$	60	16	No conv.
iii.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	16	28%
iv.	N-Ph	MeCN:H_2O (1:1)	*p*-OMe	$Pd(dppf)Cl_2$	60	16	Traces
v.	N-R[a]	H_2O	*intramol.*	$Pd(dppf)Cl_2$	60	72	31%
vi.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	100	16	Traces
vii.	N-Ph	H_2O – No PPh_3	*p*-OMe	$Pd(dppf)Cl_2$	60	16	No conv.
viii.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	40	16	Traces
ix.	N-Ph	Toluene	*p*-OMe	HBP/Cs_2CO_3	110	16	No conv.
x.	N-Ph	H_2O	*p*-CO_2Et	$Pd(dppf)Cl_2$	60	16	+O_2 (No conv.)
xi.	N-Ph	H_2O/$OPPh_3$	*p*-OMe	$Pd(dppf)Cl_2$	60	24	No conv.
xii.	N-Ph	DMF	*p*-OMe	$Pd(dppf)Cl_2$ (x2)	120	16	Traces
xiii.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	16	Traces
xiv.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$ (10%)	60	16	32%
xv.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$ (x2)	60	16	<30%[b]
xvi.	N-Ph	H_2O	*p*-OMe	$Pd(dppb)Cl_2$	60	16	<30%[b]
xvii.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	2.5	Traces[c]
xviii.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$ (x4)	60	24	<30%[d]
xix.	N-Ph[e]	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	24	Traces
xx.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	48	28%[f]
xxi.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	120	33%[g]
xxii.	N-H[h]	H_2O	*p*-OMe	$Pd(dppf)Cl_2$	60	16	No conv.
xxiii.	N-Ph	H_2O	*p*-OMe	$Pd(dppf)Cl_2$ (x2)[i]	60	2x16h	35%

a)intramol. b)not isolated c)2.5hrs d)4x 2.5% catalyst e)3x30mg pyrazole f)48hrs g) 120hrs h)free NH i)2x 5% catalyst

Following the unsuccessful optimisation studies described above, we decided to investigate the possibility of a Cu / Pd co-catalysed system as described many times before in the literature.[191] Equimolar amounts of copper in addition to a catalytic amount of palladium could prove useful for this reaction. Several copper-sources were used but none showed any improvement over the previously obtained yields of 30 - 38 % (Table 15).

Table 15. Cu / Pd-co-catalysed reaction attempts.

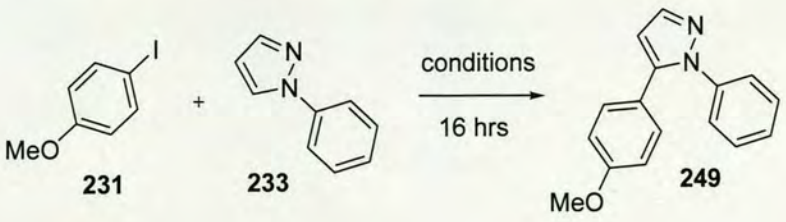


	Cu-source(1eq.)	*Base(2eq.)*	*Solv.*	*Pd-source(5%)*	Ligand	*Product*
i.	$Cu(OAc)_2$	Ag_2CO_3	H_2O	$Pd(dppf)Cl_2$	PPh_3	Traces
ii.	Cu_2O	Ag_2CO_3	H_2O	$Pd(dppf)Cl_2$	PPh_3	No conv.
iii.	$CuCl_2$	Ag_2CO_3	H_2O	$Pd(dppf)Cl_2$	PPh_3	No conv.

It was now postulated that possibly the pH and the quality of the deionised water had an influence on the rate of the reaction. Fully aware that the water in our system might solely act as a high heat-capacity agent, we designed a few reaction systems involving different water sources / pH values. Having taken pH-measurements over a 3-day period and observing a pH change from 6 to about 8.5, we knew that the pH of our system might be critical to the success of this transformation. From a mechanistic standpoint the reaction mixture certainly should be basic for the proton abstraction and β-elimination to occur. Given that two equivalents of Ag_2CO_3 are generally added to the system we expected the pH measurements to be in the basic region. Three different buffer systems (Table 16, entry *i.*, *ii.* and *iv.*) were investigated using a phosphate buffer and carbonate buffer. Entry *i.* and *ii.* both produced no detectable conversions but the buffer system at pH-13 showed a similar isolated yield as the normal 'non-buffer' conditions.

Additional modifications of our on water conditions included highly oxygenated water, deoxygenated water as well as the use of ionic liquids (Entry *iii.*, *vii.-xi.*). Ionic liquids were used with either silver carbonate or triethylamine as the base, or as a mixture of both bases (1:1). (Entry *ix.* and *x.*)

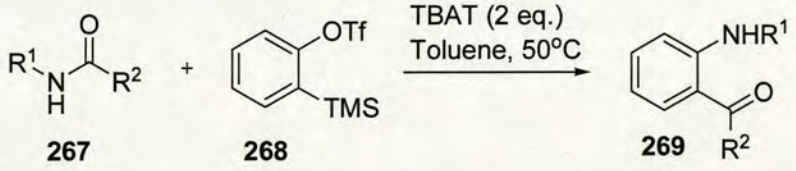
Table 16. Screen of modified on water conditions.



	Temp.	*Base*	*Solvent*	*Pd-source(5%)*	*Ligand*	*Product*
i.	60	Ag_2CO_3	Buffer pH 8.3	$Pd(dppf)Cl_2$	PPh_3	traces
ii.	60	Ag_2CO_3	Buffer pH 7.2	$Pd(dppf)Cl_2$	PPh_3	traces
iii.	60	Ag_2CO_3	H_2O (O_2)	$Pd(dppf)Cl_2$	PPh_3	29%
iv.	60	Ag_2CO_3	Buffer pH 13	$Pd(dppf)Cl_2$	PPh_3	31%
v.	60	Ag_2CO_3	H_2O (1ml)	$Pd(dppf)Cl_2$	PPh_3	28%
vi.	60	Ag_2CO_3	H_2O (5ml)	$Pd(dppf)Cl_2$	PPh_3	< 10%
vii.	60	Et_3N	Ionic liq./H_2O	$Pd(OAc)_2$	PPh_3	No conv.
viii.	60	Et_3N	Ionic liq./H_2O	$Pd(dppf)Cl_2$	PPh_3	No conv.
ix.	60	Ag_2CO_3/Et_3N	Ionic liq./H_2O	$Pd(OAc)_2$	PPh_3	No conv.
x.	60	Ag_2CO_3/Et_3N	Ionic liq./H_2O	$Pd(dppf)Cl_2$	PPh_3	No conv.
xi.	120	Et_3N	Ionic liq.	$Pd(dppf)Cl_2$	PPh_3	No conv.

Again, none of the above conditions proved to have an advantage over our original conditions. (phosphate buffer used for entry i., ii. and iv.)

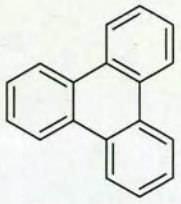
Lastly, the arylation of pyrazole was attempted using our regularly used mild benzyne conditions.[192,193]



Scheme 85. Pintori and Greaney reported the insertion of benzene rings into the amide bond.[192]

Aware that the conditions of entry *ii.* (Table 17) generate benzyne from the TMS-precursor, we set out to attempt the arylation of pyrazole. Multiple attempts were

made at ambient and slightly elevated temperatures, none of which gave any products on the LCMS or TLC. If 1-fluoro-2-bromo-benzene is used as a benzyne precursor with Mg-metal (Grignard type), heating is required to start the Grignard reaction.

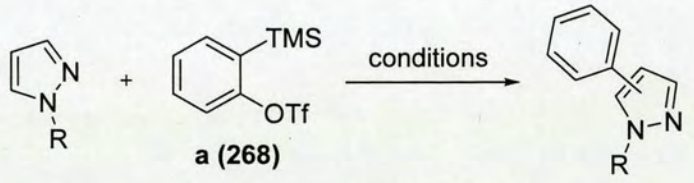


270

Figure 25. Structure of triphenylene.

This heating is unfortunately enough to trimerise the active benzyne to triphenylene, making this approach not useful.

Table 17. Benzyne-arylation trial reactions.



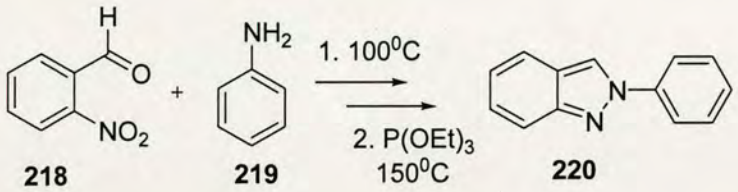
a (268)

b= 1-F,2-Br-benzene (271)

	Aryne	*Base*	*Solv.*	*Pyrazole*	Temp.	*Product*
i.	a	CsF	MeCN	N-phenyl	RT.	No conv.
ii.	a	TBAT	Toluene	N-phenyl	50°C	No conv.
iii.	a	TBAF	MeCN	N-phenyl	RT.	No conv.
iv.	a	TBAT	Toluene	N-H	50°C	No conv.
v.	a	TBAT	Toluene	N-CH_3	50°C	No conv.
vi.	b	none	THF	N-phenyl	90°C	Full conv.

2.4.3 Optimised Conditions

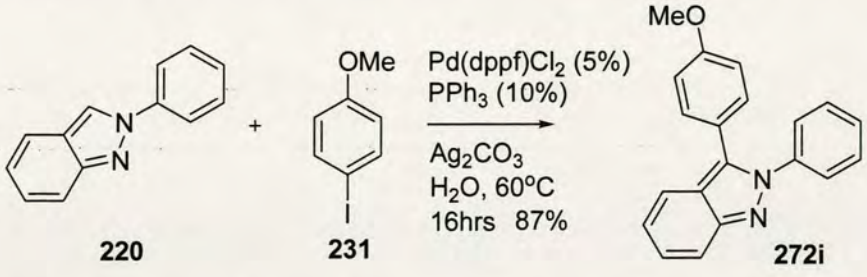
Following the discovery of a second (much rarer) tautomer of indazole in the literature, combined with our knowledge that the 5-position of pyrazole is highly reactive towards Pd-catalysed cross couplings, while the 3-position is not, we set out to synthesise 2-phenyl-2*H*-indazole.[164,154]



Scheme 86. Synthesis of 2-phenyl-2*H*-indazole.[154]

The synthesis of 2-phenyl-2*H*-indazole (**220**) proved rather challenging as the formed imine is highly light-sensitive and the purification of the final compound involved two distillations, a column and a recrystallisation. Pure 2-phenyl-2*H*-indazole (**220**) was nevertheless isolated and trial reactions began using our mild on water conditions.

The first test reaction of 2-phenyl-2*H*-indazole with 4-methoxy-iodobenzene (**231**) using the on water direct arylation conditions proved successful and the 2,3-diarylated indazole **272i** could be isolated as the only product in excellent yield.



Scheme 87. Initial direct arylation trial reaction of 2-phenyl-2*H*-indazole.

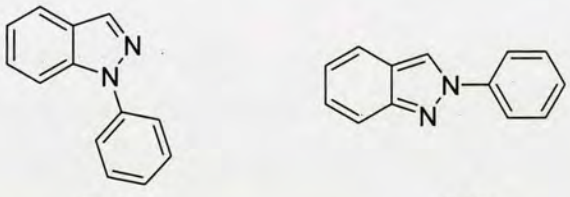
Following this early success the system was optimised. All components such as the catalyst, the base, the ligand as well as the equivalents of the starting materials were varied (quantities only) and provided the optimised conditions as described below.

Optimised conditions:

1 eq. Indazole, 1.1 eq. of arylhalide (Br / I), 1 eq. of Ag_2CO_3, 5 % catalyst, 10 % PPh_3, 3 ml of H_2O, 16 hrs at 50°C.

2.4.4 Results of On Water Methodology

We began by examining the regioisomeric 1- and 2-phenylindazoles as substrates. The C3 position is markedly less reactive towards substitution in the 1*H*-series, and this was manifested in the direct arylation studies, with 1-phenyl-1*H*-indazole undergoing no arylation at 60 °C on water under a variety of conditions. 2-Phenyl-2*H*-indazole (**220**), by contrast, proved an excellent substrate, undergoing clean on water arylation with a variety of aryl halides at 50 °C on water. (Table 18)



222
1-Phenyl-1H-indazole
(1H-series)

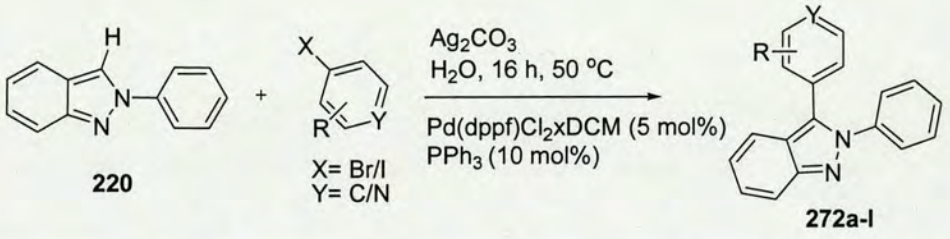
220
2-Phenyl-2H-indazole
(2H-series)

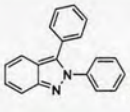
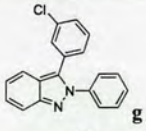
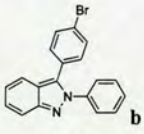
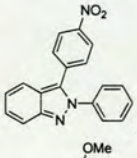
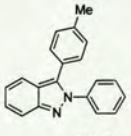
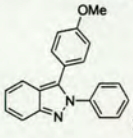
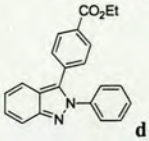
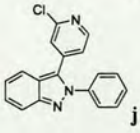
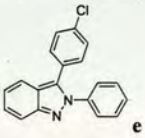
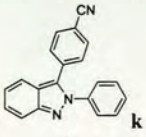
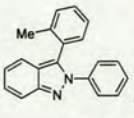
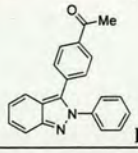
Figure 26. Phenyl-indazole regioisomers.

Our catalyst system of $Pd(dppf)Cl_2$ / PPh_3 in the presence of an equivalent of Ag_2CO_3 produced good to excellent yields of 2,3-diarylindazoles on water. The reaction was generally effective for both aryl iodides and bromides, an advance over our previous on water studies of azole heterocycles which were restricted to aryl iodides. Functional group tolerance was good, with halo (**272b**, **e**, and **g**), electron

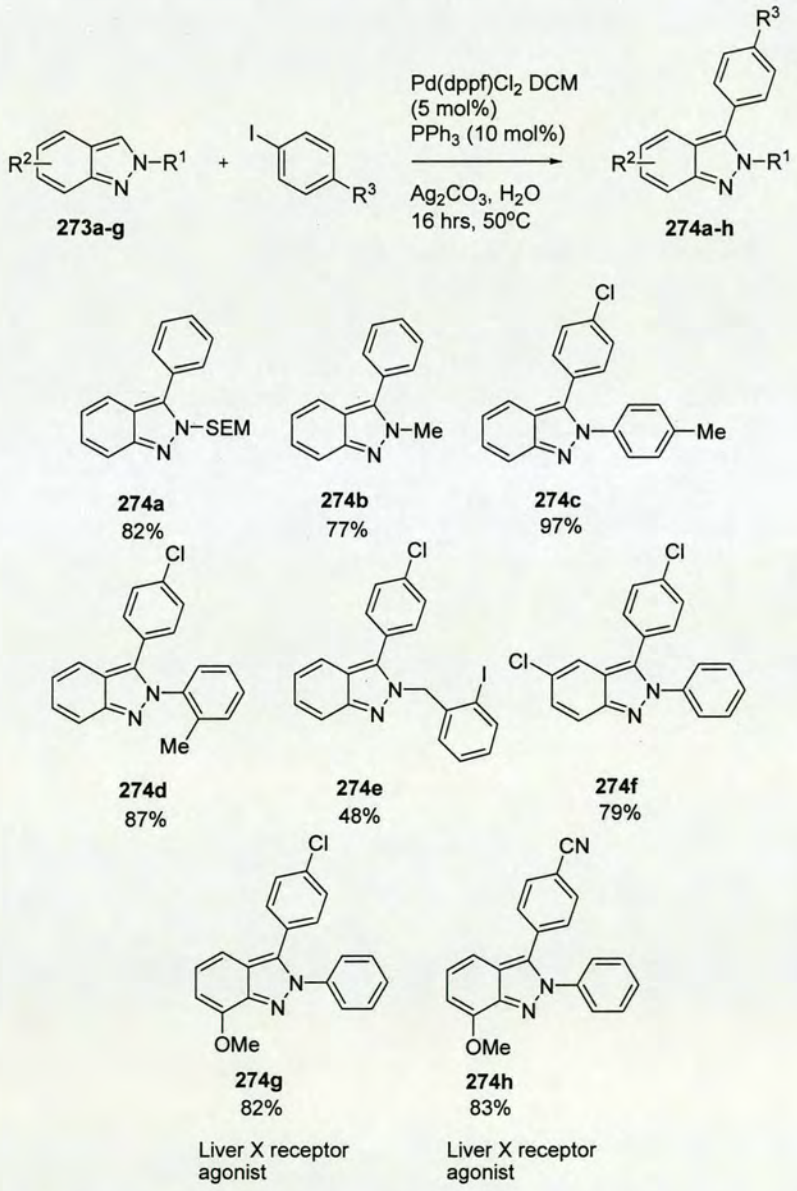
withdrawing (**272d, h, k** and **l**) and donating (**272c, f** and **i**) groups being tolerated at both *para* and *meta* positions. A single *ortho*-functionalised aryl iodide was productive, but in a diminished 49 % yield (**272f**). Heterocyclic 2-chloro-4-iodopyridine produced functionalised indazole **272j** in 95 % yield, featuring the highly versatile 2-chloropyridine functionality for further manipulation. Arylation tended to be most efficient for reactions between solids. This appears to be an artefact of mixing, in that use of liquid aryl halides can lead to a small amount adhering to the walls of the flask and not being effectively incorporated into the heterogeneous reaction mixture.

Table 18. Palladium catalysed direct arylation of 2-phenyl-2*H*-indazole on water.



Entry	Product	Yield (%)	Entry	Products	Yield (%)
1	 **272a**	76 (ArI) 71 (ArBr)	7	 **g**	96 (ArBr)
2	 **b**	80 (ArI)	8	 **h**	86 (ArBr)
3	 **c**	91 (ArI) 70 (ArBr)	9	 **i**	87 (ArI)
4	 **d**	77 (ArI) 74 (ArBr)	10	 **j**	95 (ArI)
5	 **e**	90 (From ArI) 69 (From ArBr)	11	 **k**	85 (ArI)
6	 **f**	49 (ArI)	12	 **l**	81 (ArI)

To fully establish the scope of the arylation we prepared a series of N2-substituted indazoles (**273a-g**). The SEM-protecting group proved stable to the arylation conditions, with the versatile 2-SEM protected indazole **274a** being formed in high yield. Alkyl-substituted indazoles were good substrates, as were 2-*para* and *ortho*-tolylindazoles (**274c** and **d**). The 2-iodobenzyl indazole (**273e**) starting material was prepared to examine the possibility of intramolecular cyclopentannulation via direct arylation. This reaction proved ineffective under the conditions – when 4-chloroiodobenzene was added in a competition experiment the intermolecular arylation product was isolated in moderate yield.

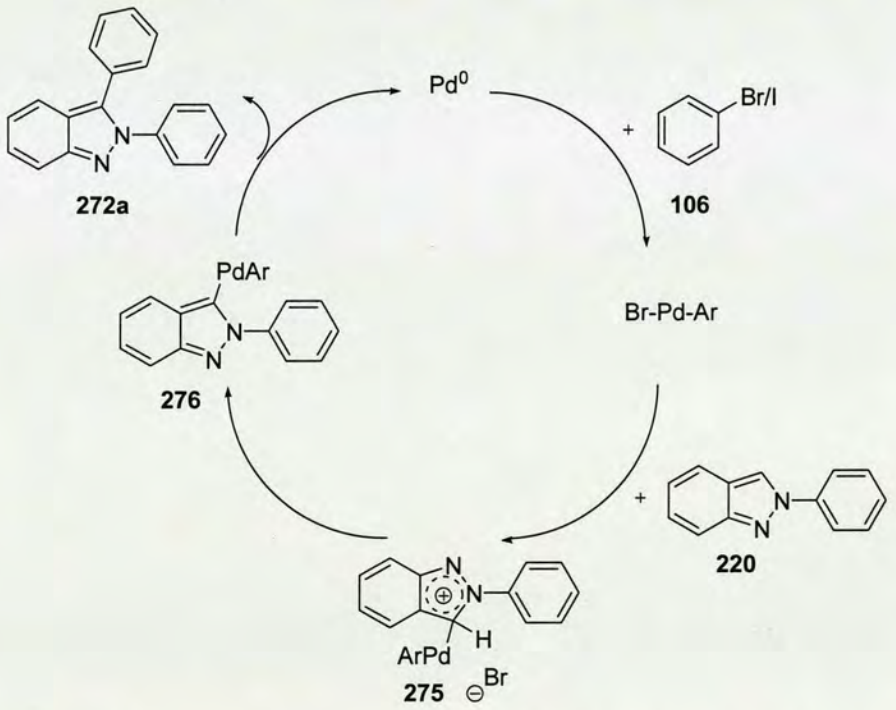


Scheme 88. Library of 2N-substituted indazoles.

Functional handles could be incorporated into the indazole ring with the 5-chloro and 7-methoxy indazole compounds being excellent substrates. Indazole **274g** and **274h** have been reported as part of a library of 1*H* and 2*H*-indazoles with activities in a range of cardiovascular diseases.[164]

2.4.5 Mechanism

The exact mechanism of this transformation is not known at this point. Early evidence shows that electron donating and electron withdrawing groups have a direct influence on the yield of this direct arylation reaction. However, the direct comparison of substituents is made more difficult by the dependence of this methodology on the morphology of the starting materials. It is suggested by us that the mechanism, very much like the mechanism of the oxazole arylations described earlier in this document, as well as Gevorgyan's and Li's, is of an electrophilic substitution nature.



Scheme 89. Likely mechanism for the direct arylation of 2-phenyl-2*H*-indazoles.

Further work on this project could aim to investigate the mechanistic origin of this transformation and the obtaining of a Hammett plot seems a logical extension of this work. Sp-sp^2 couplings were investigated, using 1-bromo-2-phenyl acetylene but did not provide any products when the 'on water' methods were applied.

2.5 Summary and Conclusions

Catalytic direct arylation of indazoles has received little attention; a single elegant study from Lautens on the synthesis of annulated 2*H*-indazoles via intramolecular direct arylation being the only extant report in the literature.[172] In summary, we have reported the first study of an intermolecular direct arylation of indazoles. Using on water reaction conditions, a simple and efficient protocol has been developed that produces diverse C3-arylated indazoles under notably mild conditions.[194]

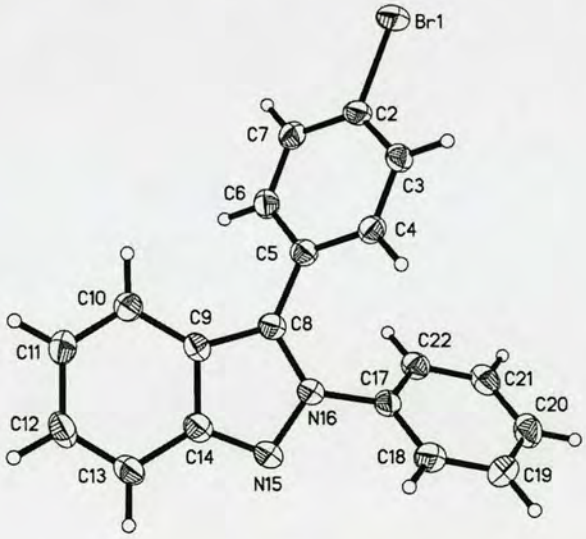


Figure 27. X-ray structural analysis showing C3-arylation of 2-phenyl-2*H*-indazole to **272b**.

This methodology provides rapid access to this important class of molecules. Furthermore, these reactions were investigated on a larger scale and proved to be effective for transformation of 0.9 g of indazole starting material **273c** to give 2,3-diaryl-2*H*-indazole **274c** in 78 % yield. Improvements from the earlier published

conditions include the use of aryl bromides instead of aryl iodides, the use of only one equivalent of silver base as well as the reduced amount of aryl halides used.[182] Finally, the reaction temperature of 60 °C applied for the oxazole direct arylations was lowered to an even milder 50 °C in the case of most indazole arylations.

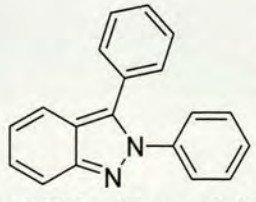
2.6 Experimental

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brüker dpx360 (360 MHz), Brüker dpx250 (250MHz) as well as a Brüker ava800 (800 MHz) instruments. Melting point measurements were obtained from a Gallenkamp melting point apparatus and are uncorrected. Electrospray high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer. The data is recorded as the ionisation method followed by the calculated and measured masses. TLC was performed on Merck $60F_{254}$ silica plates and visualized by UV light. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. Distilled water was used in reactions carried out in water as the solvent.

Representative procedure for the direct arylation of 2H-Aryl-indazoles with aryl iodides and aryl bromides on water:

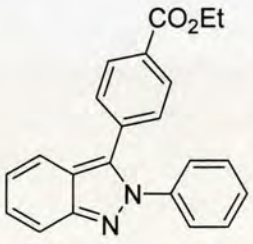
2,3-Diphenyl-2H-indazole (272a)



A 5 mL microwave vial was charged with 2-Phenyl-2*H*-indazole (50 mg, 0.26 mmol, 1 equiv.), phenyliodide (57 mg, 0.28 mmol, 1.1 equiv.), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (11 mg, 0.013mmol, 5 mol %), Ag_2CO_3 (72 mg, 0.26 mmol, 1 equiv.) and PPh_3 (7 mg, 0.026 mmol, 10 mol %). A magnetic stirrer bar was added and the mixture of solids was gently shaken for a few seconds to ensure all solids were well

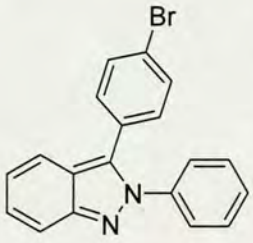
mixed. Distilled water (3 mL) was added and the vial was covered with a serum cap. The vial and its contents were then heated and stirred in a pre-heated oil bath at 50 °C for 16 h. After this time the reaction mixture was cooled down to rt. CH_2Cl_2 (4 ml) was added and the contents of the vial were filtered through a short pad of celite. The vial was rinsed once with an additional 1 mL of CH_2Cl_2. The organic layer was separated, and the aqueous phase extracted once with CH_2Cl_2. The organic layers were combined and concentrated *in vacuo*. The residue was purified by flash chromatography (silica, hexane / CH_2Cl_2 1:1) and provided the title compound in 76 % yield as a white solid. Best purification results were obtained when a gradient from hexane (100 %) to CH_2Cl_2 (100 %) was applied. Alternatively, other similar sized glass vials can be used as a reaction vessel. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.83 (1H, d, *J*= 7.2Hz), 7.73 (1H, d, *J*= 7.2Hz), 7.47-7.36 (12H, m), 7.17-7.13 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.9 (quat), 140.2 (quat), 135.4 (quat), 129.8 (quat), 129.6 (2xCH), 128.9 (2xCH), 128.7 (2xCH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 126.0 (2xCH), 122.5 (CH), 121.7 (quat), 120.5 (CH), 117.7 (CH). **Mp.** 102-103°C. **HRMS** (ESI) calculated for $C_{19}H_{15}N_2$ (MH^+), 271.1230; found 271.1232.

Ethyl-4-(2-phenyl-2H-indazol-3-yl)benzoate (272d)



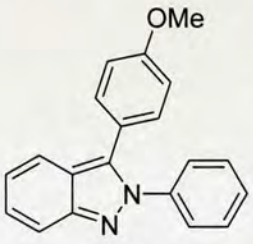
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272d** as an off-white solid (77 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.97 (2H, d, *J*= 7.2Hz), 7.73 (1H, d, *J*= 7.2Hz), 7.61 (1H, d, *J*= 7.2Hz), 7.34-7.28 (8H, m), 7.07 (1H, t, *J*= 7.2Hz), 4.30 (2H, q, *J*= 7.2Hz, *J*= 14.4Hz), 1.30 (3H, t, *J*= 7.2Hz). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 165.9 (quat), 148.9 (quat), 139.8 (quat), 134.1 (quat), 134.0 (quat), 129.9 (quat), 129.8 (2xCH), 129.3 (2xCH), 129.0 (2xCH), 128.4 (CH), 127.0 (CH), 125.9 (2xCH), 123.0 (CH), 121.8 (quat), 120.0 (CH), 117.8 (CH), 61.1 (CH_2), 14.2 (CH_3). **Mp.** 150-153°C. **HRMS** (ESI) calculated for $C_{22}H_{19}N_2O_2$ (MH^+), 343.1441; found 343.1449.

3-(4-Bromophenyl)-2-phenyl-2H-indazole (272b)



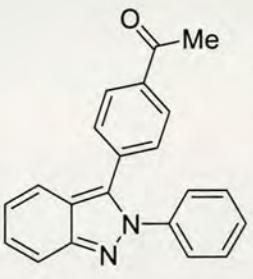
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272b** as a white solid (80 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.81 (1H, d, *J*= 7.2Hz), 7.68 (1H, d, *J*= 7.2Hz), 7.55-7.52 (2H, m), 7.44-7.36 (6H, m), 7.24-7.15 (3H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.9 (quat), 139.9 (quat), 134.1 (quat), 132.1 (2xCH), 131.1 (2xCH), 129.2 (2xCH), 128.8 (quat), 128.5 (CH), 127.1 (CH), 126.0 (2xCH), 122.9 (CH), 122.7 (quat), 121.6 (quat), 120.1 (CH), 117.9 (CH). **Mp.** 109-110°C. **HRMS** (EI) calculated for $C_{19}H_{12}N_2Br$ $(M-H)^+$, 347.0178; found 347.0182.

3-(4-Methoxyphenyl)-2-phenyl-2H-indazole (272i)



Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272i** as a light brown oil (87 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.70 (1H, d, *J*= 7.2Hz), 7.60 (1H, d, *J*= 7.2Hz), 7.37-7.16 (8H, m), 7.025 (1H, t, *J*= 9Hz), 6.82 (2H, d, *J*= 7.2Hz), 3.73 (3H, s, CH_3). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 159.5 (quat), 148.9 (quat), 140.3 (quat), 135.3 (quat), 130.9 (2xCH), 128.9 (2xCH), 128.1 (CH), 126.9 (CH), 125.9 (2xCH), 122.1 (quat), 122.0 (CH), 121.5 (quat), 120.6 (CH), 117.6 (CH), 114.2 (2xCH), 55.2 (CH_3). **HRMS** (EI) calculated for $C_{20}H_{16}N_2O$ (M^+), 300.1257; found 300.1255.

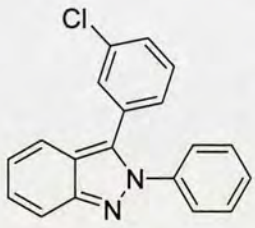
1-(4-(2-Phenyl-2H-indazol-3yl)phenyl)ethanone (272l)



Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272l** as a light yellow solid (81 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.975 (2H, d, *J*= 10.8Hz), 7.83 (1H, d, *J*= 7.2Hz), 7.725 (1H, d, *J*= 10.8Hz),

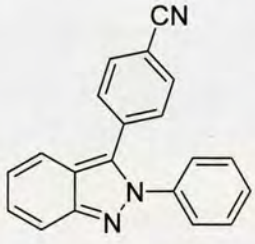
7.47-7.37 (8H, m), 7.19 (1H, t, *J*= 7.2Hz), 2.62 (3H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 197.3 (quat), 149.0 (quat), 139.9 (quat), 136.3 (quat), 134.4 (quat), 134.0 (quat), 129.6 (2xCH), 129.2 (2xCH), 128.7 (2xCH), 128.6 (CH), 127.2 (CH), 126.0 (2xCH), 123.2 (CH), 121.9 (quat), 120.0 (CH), 118.0 (CH), 26.6 (CH_3). **Mp.** 136-138°C. **HRMS** (ESI) calculated for $C_{21}H_{17}N_2O$ (MH^+), 313.1335; found 313.1327.

3-(3-Chlorophenyl)-2-phenyl-2H-indazole (272g)



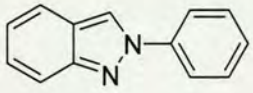
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane/DCM 1:1) to afford the coupled product **272g** as an off-white solid (96 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.77 (1H, d, *J*= 7.2Hz), 7.65 (1H, d, *J*= 7.2Hz), 7.39-7.10 (11H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.9 (quat), 139.8 (quat), 134.6 (quat), 133.7 (quat), 131.6 (quat), 130.0 (CH), 129.4 (CH), 129.1 (2xCH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 125.9 (2xCH), 123.0 (CH), 121.7 (quat.), 120.0 (CH), 117.9 (CH). **Mp.** 95-96°C. **HRMS** (EI) calculated for $C_{19}H_{12}N_2Cl$ $(M-H)^+$, 303.0684; found 303.0683.

3-(4-Cyanophenyl)-2-phenyl-2H-indazole (272k)



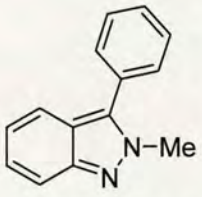
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272k** as a white solid (85 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.74 (1H, d, *J*= 7.2Hz), 7.62-7.57 (3H, m), 7.39-7.17 (8H, m), 7.14-7.10 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 149.0 (quat), 139.6 (quat), 134.4 (quat), 133.0 (quat), 132.4 (2xCH), 129.9 (2xCH), 129.3 (2xCH), 128.8 (CH), 127.2 (CH), 126.0 (2xCH), 123.6 (CH), 121.8 (quat), 119.6 (CH), 118.3 (quat), 118.1 (CH), 111.7 (quat). **Mp.** 152-153°C. **HRMS** (ESI) calculated for $C_{20}H_{14}N_3$ (MH^+), 296.1182; found 296.1184.

2-Phenyl-2H-indazole (220)



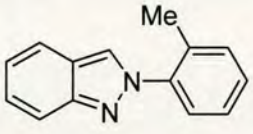
This is a known compound.[195] NMR data matched the literature values. This compound was isolated as a light yellow oil in 12% lower yield than reported previously. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.33 (1H, s), 7.83 (2H, d, *J*= 7.2Hz), 7.72 (1H, d, *J*= 7.2Hz), 7.63 (1H, d, *J*= 7.2Hz), 7.45 (2H, t, *J*= 7.2Hz), 7.32 (1H, t, *J*= 7.2Hz), 7.24 (1H, t, *J*= 7.2Hz), 7.04 (1H, t, *J*= 7.2Hz). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 149.8 (quat), 140.5 (quat), 129.5 (2xCH), 127.9 (CH), 126.8 (CH), 122.7 (quat), 122.4 (CH), 121.0 (2xCH), 120.4 (CH), 120.4 (CH), 117.9 (CH).

2-Methyl-3-phenyl-2H-indazole (274b)



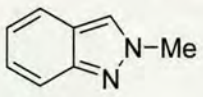
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274b** as a light yellow oil (77 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.74-7.70 (1H, m), 7.61-7.46 (6H, m), 7.35-7.12 (1H, m), 7.09-7.06 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.0 (quat), 136.0 (quat), 129.6 (quat), 129.5 (2xCH), 129.0 (2xCH), 128.7 (CH), 126.2 (CH), 121.8 (CH), 121.1 (quat), 120.1 (CH), 116.9 (CH), 38.5 (CH_3). **HRMS** (ESI) calculated for $C_{14}H_{13}N_2$ (MH^+), 209.1073; found 209.1076.

2-*o*-Tolyl-2H-indazole (273d)



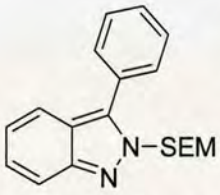
This is a known compound.[195] NMR data matched the literature values. This compound was isolated as a light yellow oil with a yield 21% below the literature value. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.11 (1H, s), 7.81 (1H, d, *J*= 7.2Hz), 7.75 (1H, d, *J*= 7.2Hz), 7.45-7.33 (5H, m), 7.15 (1H, t, *J*= 7.2Hz), 2.25 (3H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 149.2 (quat), 140.3 (quat), 133.9 (quat), 131.2 (CH), 129.1 (CH), 126.6 (CH), 126.5 (CH), 126.3 (CH), 124.3 (CH), 122.1 (CH), 121.9 (quat), 120.3 (CH), 117.9 (CH), 17.8 (CH_3). **HRMS** (ESI) calculated for $C_{14}H_{13}N_2$ (MH^+), 209.1073; found 209.1072.

2-Methyl-2H-indazole (273b)



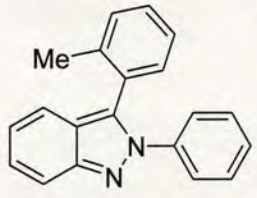
This is a known compound.[196] NMR data matched the literature values. The compound was isolated as a colourless oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.86 (1H, s), 7.67-7.61 (2H, m), 7.30-7.23 (1H, m), 7.10-7.04 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 149.0 (quat.), 125.8 (CH), 123.5 (CH), 122.0 (quat.), 121.6 (CH), 119.9 (CH), 117.1 (CH), 40.3 (CH_3).

2-((2-Trimethylsilyl)ethoxy)methyl)-3-phenyl-2H-indazole (274a)



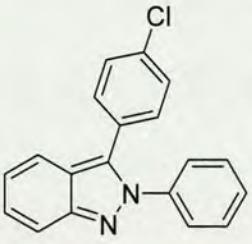
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274a** as a yellow oil (82 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.78-7.75 (3H, m), 7.69 (1H, d, *J*= 7.2Hz), 7.56 (2H, t, *J*= 7.2Hz), 7.50-7.46 (1H, m), 7.35 (1H, t, *J*= 7.2Hz), 7.11 (1H, t, *J*= 7.2Hz), 5.71 (2H, s), 3.85 (2H, t, *J*= 7.2Hz), 0.97 (2H, t, *J*=7.2Hz), 0.00 (9H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.2 (quat), 136.9 (quat), 129.8 (2xCH), 129.5 (quat), 129.0 (2xCH), 128.8 (CH), 126.8 (CH), 122.3 (CH), 121.2 (CH), 120.8 (CH), 117.8 (CH), 79.2 (CH_2), 67.6 (CH_2), 18.0 (CH_2), -1.4 ($3xCH_3$) **HRMS** (ESI) calculated for $C_{19}H_{25}N_2OSi$ (MH^+), 325.1731; found 325.1725.

2-Phenyl-3-o-tolyl-2H-indazole (272f)



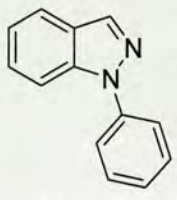
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / CH_2Cl_2 1:1) to afford the coupled product **272f** as a light brown solid (49 % yield). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.825 (1H, d, *J*= 8.0Hz), 7.445 (1H, d, *J*= 8.0Hz), 7.41 (2H, d, *J*= 8.0Hz), 7.38-7.25 (8H, m), 7.10 (1H, t, *J*= 8.0Hz), 1.95 (3H, s). **^{13}C NMR** (200 MHz, $CDCl_3$), δ 148.7 (quat), 140.3 (quat), 137.8 (quat), 135.4 (quat), 131.1 (CH), 130.6 (CH), 129.5 (quat), 129.3 (CH), 128.9 (2xCH), 127.9 (CH), 127.1 (CH), 126.0 (CH), 124.8 (2xCH), 122.5 (quat), 122.1 (CH), 120.7 (CH), 117.6 (CH), 19.9 (CH_3). **Mp**. 92-93°C, **HRMS** (ESI) calculated for $C_{20}H_{17}N_2$ (MH^+), 285.1386; found 285.1387.

3-(4-Chlorophenyl)-2-phenyl-2H-indazole (272e)



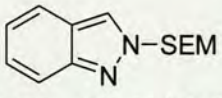
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane/DCM 1:1) to afford the coupled product **272e** as a white solid (90 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.77 (1H, d, *J*= 7.2Hz), 7.64 (1H, d, *J*= 7.2Hz), 7.40-7.22 (10H, m), 7.15-7.10 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.9 (quat), 139.9 (quat), 134.4 (quat), 134.1 (quat), 130.8 (2xCH), 129.1 (4xCH), 128.5 (CH), 128.3 (quat.), 127.1 (CH), 126.0 (2xCH), 122.8 (CH), 121.7 (quat), 120.1 (CH), 117.9 (CH). **Mp.** 134-135°C. **HRMS** (EI) calculated for $C_{19}H_{12}N_2Cl$ $(M-H)^+$, 303.0684; found 303.0682.

1-Phenyl-1H-indazole (222)



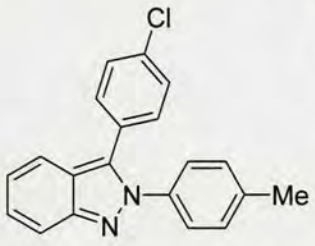
This is a known compound.[197] NMR data matched the literature values. This compound was isolated as a white solid. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.89 (1H, s), 7.36 (2H, t, *J*= 7.2Hz), 7.32-7.27 (1H, m), 7.21 (1H, d, *J*= 7.2Hz), 7.05 (3H, t, *J*= 7.2Hz), 7.00-6.93 (2H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 157.0 (quat), 143.3 (quat), 141.2 (CH), 130.0 (CH), 129.5 (2xCH), 129.3 (CH), 120.9 (CH), 119.4 (CH), 118.5 (quat), 116.6 (CH), 112.6 (CH).

2-((2-(Trimethylsilyl)ethoxy)methyl)-2H-indazole (273a)



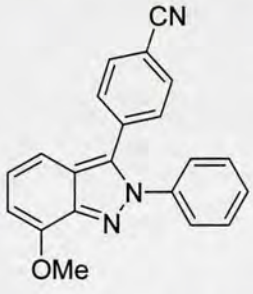
This is a known compound.[198] NMR data matched the literature values. Compound was isolated as a colourless oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.11 (1H, s), 7.75-7.67 (2H, m), 7.30 (1H, t, *J*= 7.2Hz), 7.10 (1H, t, *J*= 7.2Hz), 5.73 (2H, s), 3.63 (2H, t, *J*= 7.2Hz), 0.94 (2H, t, *J*= 7.2Hz), -0.03 (9H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.8 (quat), 126.4 (CH), 122.6 (CH), 122.2 (quat), 122.1 (CH), 120.5 (CH), 117.9 (CH), 81.8 (CH_2), 67.5 (CH_2), 17.9 (CH_2), -1.50 ($3xCH_3$).

3-(4-Chlorophenyl)-2-*p*-tolyl-2H-indazole (274c)



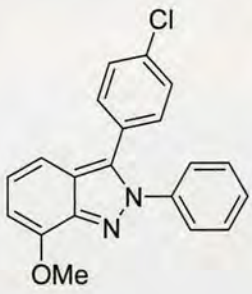
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274c** as a light yellow solid (97 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.81 (1H, d, *J*= 7.2Hz), 7.67 (1H, d, *J*= 7.2Hz), 7.39-7.27 (7H, m), 7.21-7.13 (3H, m), 2.40 (3H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.8 (quat), 138.5 (quat), 137.4 (quat), 134.3 (quat), 133.9 (quat), 130.8 (2xCH), 129.7 (2xCH), 129.0 (2xCH), 128.4 (quat), 126.9 (CH), 125.7 (2xCH), 122.7 (CH), 121.6 (quat), 120.0 (CH), 117.8 (CH), 21.1 (CH_3). **Mp.** 124-126°C. **HRMS** (ESI) calculated for $C_{20}H_{16}N_2Cl$ (MH^+), 319.0997; found 319.0998.

3-(4-Cyanophenyl)-7-methoxy-2-phenyl-2H-indazole (274h)



Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274h** as a white solid (83 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.65 (2H, d, *J*= 7.2Hz), 7.44 (2H, d, *J*= 7.2Hz), 7.41-7.36 (5H, m), 7.24 (1H, d, *J*= 7.2Hz), 7.11 (1H, t, *J*= 7.2Hz), 6.65 (1H, d, *J*= 7.2Hz), 4.05 (3H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 150.5 (quat), 142.6 (quat), 139.6 (quat), 134.5 (quat), 133.1 (quat), 132.4 (2xCH), 129.9 (2xCH), 129.1 (2xCH), 128.7 (CH), 126.2 (2xCH), 124.4 (CH), 123.4 (quat), 118.3 (quat), 111.6 (quat), 111.3 (CH), 103.5 (CH), 55.5 (CH_3). **Mp.** 185-186°C. **HRMS** (ESI) calculated for $C_{21}H_{16}N_3O$ (MH^+), 326.1288; found 326.1288.

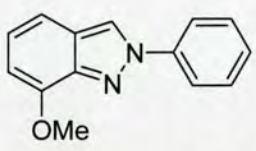
3-(4-Chlorophenyl)-7-methoxy-2-phenyl-2H-indazole (274g)



Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274g** as a white solid (82% yield). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.65-7.41 (10H, m),

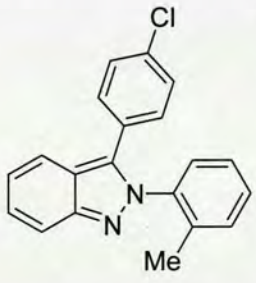
7.26 (1H, t, *J*= 7.5Hz), 6.825 (1H, d, *J*= 7.5Hz), 4.24 (3H, s). **^{13}C NMR** (63 MHz, $CDCl_3$), δ 150.4 (quat), 142.5 (quat), 139.9 (quat), 134.3 (quat), 134.2 (quat), 130.8 (2xCH), 129.0 (2xCH), 128.9 (2xCH), 128.4 (CH), 128.4 (quat), 126.2 (2xCH), 123.5 (CH), 123.2 (quat), 111.9 (CH), 103.3 (CH), 55.5 (CH_3). **Mp.** 129-131°C. **HRMS** (ESI) calculated for $C_{20}H_{16}ClN_2O$ (MH^+), 335.0946; found 335.0947.

7-Methoxy-2-phenyl-2H-indazole (273g)



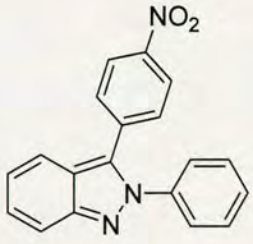
This compound was synthesised according to a known procedure.[195] The residue was purified by flash chromatography (CH_2Cl_2, 100 %) to afford the coupled product **273g** as a brown oil (44 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.42 (1H, s), 7.98 (2H, d, *J*= 7.2Hz), 7.55 (2H, t, *J*= 7.2Hz), 7.42 (1H, t, *J*= 7.2Hz), 7.315 (1H, d, *J*= 7.2Hz), 7.07 (1H, t, *J*= 7.2Hz), 6.63 (1H, d, *J*= 7.2Hz), 4.10 (3H, s). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 150.4 (quat), 143.3 (quat), 140.4 (quat), 129.3 (2xCH), 127.8 (CH), 124.3 (quat), 123.1 (CH), 121.0 (2xCH), 120.5 (CH), 112.3 (CH), 103.1 (CH), 55.4 (CH_3). **HRMS** (ESI) calculated for $C_{14}H_{13}N_2O$ (MH^+), 225.1022; found 225.1019.

3-(4-Chlorophenyl)-2-*o*-tolyl-2H-indazole (274d)



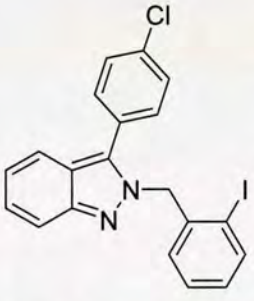
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274d** as a light brown oil (87 % yield). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.00-7.91 (2H, m), 7.60-7.33 (10H, m), 2.10 (3H, s). **^{13}C NMR** (63 MHz, $CDCl_3$), δ 148.8 (quat), 139.1 (quat), 135.3 (quat), 135.0 (quat), 134.2 (quat), 131.0 (CH), 130.1 (2xCH), 129.5 (CH), 129.0 (2xCH), 128.1 (quat), 127.9 (CH), 126.8 (CH), 126.6 (CH), 122.7 (CH), 120.5 (quat), 120.1 (CH), 118.0 (CH), 17.5 (CH_3). **HRMS** (ESI) calculated for $C_{20}H_{16}N_2Cl$ (MH^+), 319.0997; found 319.1000.

3-(4-Nitrophenyl)-2-phenyl-2H-indazole (272h)



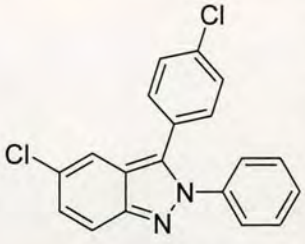
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272h** as a yellow solid (86% yield). **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.225 (2H, d, *J*= 7.5Hz), 7.845 (1H, d, *J*= 7.5Hz), 7.725 (1H, d, *J*= 7.5Hz), 7.525 (2H, d, *J*= 7.5Hz), 7.46-7.39 (6H, m), 7.25-7.21 (1H, m). **^{13}C NMR** (63 MHz, $CDCl_3$), δ 149.1 (quat), 147.1 (quat), 139.6 (quat), 136.3 (quat), 132.7 (quat), 130.1 (2xCH), 129.4 (2xCH), 128.9 (CH), 127.3 (CH), 126.0 (2xCH), 124.0 (2xCH), 123.9 (CH), 122.0 (quat), 119.5 (CH), 118.2 (CH). **Mp.** 160-162°C. **HRMS** (ESI) calculated for $C_{19}H_{14}N_3O_2$ (MH^+), 316.1081; found 316.1079.

2-(2-Iodobenzyl)-3-(4-Chlorophenyl)-2H-indazole (274e)



Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274e** as an orange solid (48% yield). **^{1}H NMR** (800 MHz, $CDCl_3$) δ 7.85 (1H, dd, *J*= 7.8Hz, 7.8Hz), 7.76-7.78 (1H, m), 7.61-7.60 (1H, m), 7.47-7.45 (2H, m), 7.38-7.36 (1H, m), 7.34-7.32 (2H, m), 7.22 (1H, dt, *J*= 7.2Hz), 7.15 (1H, ddd, *J*= 7.2Hz), 6.99-6.97 (1H, m), 6.55-6.54 (1H, m), 5.61 (2H, s). **^{13}C NMR** (200 MHz, $CDCl_3$), δ 148.5 (quat), 139.4 (CH), 139.2 (quat), 135.7 (quat), 135.2 (quat), 130.5 (2xCH), 129.5 (2xCH), 129.4 (CH), 128.8 (CH), 127.7 (quat), 127.5 (CH), 126.8 (CH), 122.5 (CH), 121.2 (quat), 120.1 (CH), 117.6 (CH), 96.3 (quat), 59.4 (CH_2). **Mp**. 196-198°C. **HRMS** (ESI) calculated for 444.9963 $C_{20}H_{15}ClN_2I$ (MH^+), found 444.9960.

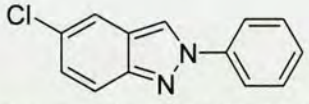
5-Chloro-3-(4-Chlorophenyl)-2-phenyl-2H-indazole (274f)



Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **274f** as a

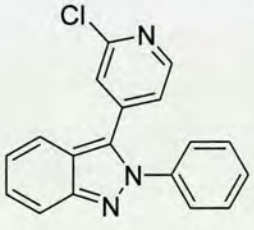
light yellow oil (79 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.36 (1H, s), 7.88 (2H, d, *J*= 7.2Hz), 7.75-7.69 (2H, m), 7.54 (2H, t, *J*= 7.2Hz), 7.42 (1H, t, *J*= 7.2Hz), 7.27-7.24 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 147.2 (quat), 139.6 (quat), 134.7 (quat), 133.8 (quat), 130.7 (2xCH), 129.2 (4xCH, quat), 128.7 (CH), 128.5 (CH), 127.7 (quat), 125.8 (2xCH), 122.0 (quat), 119.4 (CH), 118.8 (CH). **HRMS** (ESI) calculated for $C_{19}H_{13}N_2Cl_2$ (MH^+), 339.0450; found 339.0452.

5-Chloro-2-phenyl-2H-indazole (273f)



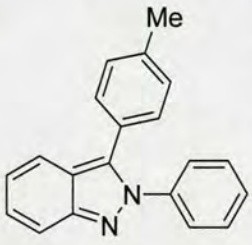
This is a known compound.[199] NMR data matched the literature values. This compound was isolated as a light brown solid. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 8.42 (1H, s), 7.975 (2H, d, *J*= 7.5Hz), 7.845 (1H, d, *J*= 7.5Hz), 7.765 (1H, d, *J*= 2.5Hz), 7.63 (2H, t, *J*= 7.5Hz), 7.52 (1H, t, *J*= 7.5Hz), 7.39-7.34 (1H, dd, *J*= 10.0Hz, 2.5Hz). **^{13}C NMR** (63 MHz, $CDCl_3$), δ 148.0 (quat), 140.1 (quat), 129.5 (2xCH), 128.1 (2x overlapping CH), 128.0 (quat), 123.0 (quat) 120.8 (2xCH), 119.9 (CH), 119.4 (CH), 119.0 (CH). **Mp**. 146-148°C.

3-(2-Chloropyridin-4-yl)-2-phenyl-2H-indazole (272j)



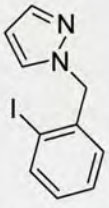
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272j** as a yellow solid (95% yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 8.375 (1H, d, *J*= 3.6Hz), 7.86 (1H, d, *J*= 7.2Hz), 7.755 (1H, d, *J*= 10.8Hz), 7.50-7.38 (6H, m), 7.29-7.25 (1H, m), 7.11-7.09 (1H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 152.1 (quat), 149.9 (CH), 149.1 (quat), 140.5 (quat), 139.4 (quat), 130.7 (quat), 129.5 (2xCH), 129.2 (CH), 127.3 (CH), 126.0 (2xCH), 124.2 (CH), 123.7 (CH), 122.2 (CH), 122.0 (quat), 119.3 (CH), 118.4 (CH). **Mp**. 130-132°C, **HRMS** (ESI) calculated for $C_{18}H_{13}ClN_3$ (MH^+), 306.0793; found 306.0793.

2-Phenyl-3-*p*-tolyl-2H-indazole (272c)



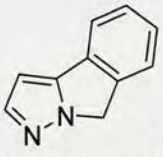
Synthesised according to the general procedure. The residue was purified by flash chromatography (silica, hexane / DCM 1:1) to afford the coupled product **272c** as an off-white solid (91 % yield). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.715 (1H, d, *J*= 7.2Hz), 7.63 (1H, d, *J*= 7.2Hz), 7.38-7.18 (6H, m), 7.11-7.03 (5H, m). **^{13}C NMR** (90 MHz, $CDCl_3$), δ 148.9 (quat), 140.3 (quat), 138.3 (quat), 135.5 (quat), 129.5 (4xCH), 128.9 (2xCH), 128.2 (CH), 126.9 (CH), 126.9 (quat), 122.3 (CH), 121.6 (quat), 120.6 (CH), 117.6 (CH), 21.3 (CH_3). **Mp**. 108-110°C **HRMS** (EI) calculated for $C_{20}H_{16}N_2$ (M^+), 284.1308; found 284.1309.

1-(2-Iodobenzyl)-1*H*-pyrazole (264)



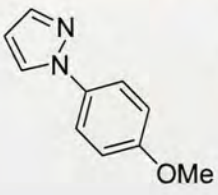
Synthesised according to a known procedure.[186] **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.86 (1H, d, *J*= 5 Hz), 7.60 (1H, s), 7.47 (1H, s), 7.28 (1H, t, *J*= 5Hz), 7.00 (1H, t, *J*= 5Hz), 6.67 (1H, d, *J*= 5Hz), 6.32 (1H, s) 5.38 (2H, s). **^{13}C NMR** (200 MHz, $CDCl_3$) δ 139.9 (CH), 139.5 (CH), 139.3 (quat), 129.9 (CH), 129.6 (CH), 128.9 (CH), 128.8 (CH), 106.0 (CH), 100.8 (quat), 60.3 (CH).

8*H*-Pyrazolo[5,1-a]isoindole (265)



Synthesised according to the general procedure (reaction temperature 60°C instead of 50°C). **^{1}H NMR** (360 MHz, $CDCl_3$) δ 7.65 (1H, s), 7.60 (1H, d, *J*= 7.3Hz) , 7.45-7.32 (3H, m), 6.38 (1H, s), 5.11 (2H, s). **^{13}C NMR** (90 MHz, $CDCl_3$) δ 146.3 (quat), 143.6 (CH), 140.5 (quat), 131.0 (quat), 128.2 (CH), 127.2 (CH), 123.5 (CH), 120.5 (CH), 96.4 (CH), 52.1 (CH_2).

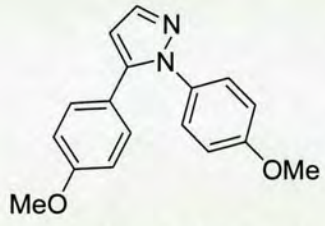
1-(4-Methoxyphenyl)-pyrazole (232)



A round bottomed flask (evacuated and back-filled with nitrogen) was charged with $Fe(acac)_3$ (212 mg, 0.6 mmol), CuO (16 mg, 0.2

mmol), pyrazole (205 mg, 3.0 mmol), and Cs_2CO_3 (1.3 g, 4.0 mmol). 4-Methoxyiodobenzene (468 mg, 2.0 mmol, 1 equiv.) was added under nitrogen, followed by anhydrous DMF (2 mL). The tube was sealed under nitrogen, and the mixture was heated to 90 °C and stirred for 24 hrs. After cooling to room temperature, the mixture was diluted with DCM and filtered through a celite filter funnel. The filtrate was washed twice with water, and the combined aqueous phases were extracted twice with DCM (2x 15 ml). The organic layers were combined, dried over $MgSO_4$, and concentrated to yield the crude product, which was further purified by silica gel chromatography (1:1 hexanes / DCM) to yield 1-(4-methoxyphenyl)-pyrazole (**232**) as a yellow oil (486 mg, 90 % yield); **^{1}H NMR** (600 MHz; $CDCl_3$) δ 7.81 (1H, d, *J*= 2.4 Hz), 7.69 (1H, *J*= 2.4 Hz), 7.58 (2H, d, *J*= 12 Hz), 6.96 (2H, d, *J*= 12 Hz), 6.42 (1H, t, *J*= 4.2 Hz). Spectral data matched literature values.[166] (from B.Sc. thesis of C.Stubbs)

1-(4-Methoxyphenyl)-5-(4-methoxyphenyl)-pyrazole (248)



Prepared according to the general procedure using 2 equivalents of the aryl iodide. Purification by silica gel chromatography (DCM, 100 %) gave the pure product **248** as a dark yellow solid (33 % yield, Mp. 93-96 °C); **^{1}H NMR** (250 MHz; $CDCl_3$) δ 7.68 (1H, d, *J*= 1.5 Hz), 7.25-7.14 (4H, m), 6.89-6.82 (4H, m), 6.45 (1H, d, *J*= 2.5 Hz), 3.82 (3H, s), 3.81 (3H, s). **^{13}C NMR** (62.5 MHz; $CDCl_3$) δ 159.3 (quat), 158.6 (quat), 142.7 (quat), 139.8 (CH), 133.4 (quat), 129.9 (2x CH), 126.5 (2x CH), 123.0 (quat), 114.0 (2x **C**H), 113.8 (2x CH), 106.7 (CH), 55.4 (CH_3), 55.2 (CH_3). **HRMS** (EI) *m/z* calcd for $C_{17}H_{16}O_2N_2$ 280.1206, found 280.1205. (from B.Sc. thesis of C.Stubbs)

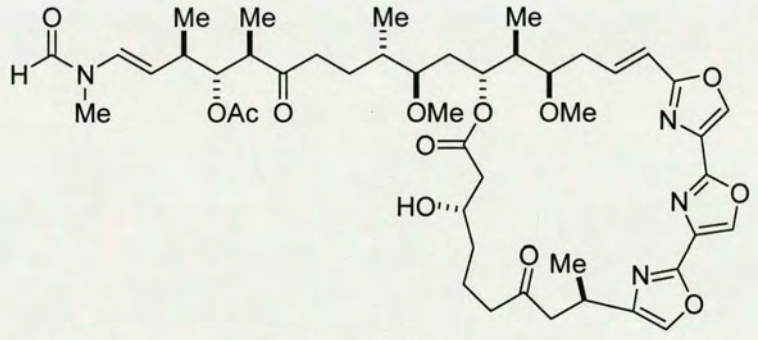
Chapter 3.

Towards the Total Synthesis of Mechercharmycin A

3.1 Introduction

3.1.1 Polyoxazole Containing Natural Products

Naturally occurring oxazoles were uncommon until about 20 years ago when several natural products containing the oxazole moiety were isolated from marine microorganisms.[39] Marine organisms have long been recognised as potent sources for potential lead compounds, which could be developed into new pharmaceuticals.[200] Two interesting structures isolated in the 1980's include hennoxazole A (as described in chapter one of this thesis) as well as ulapualide A. (Figure 28, **277**)

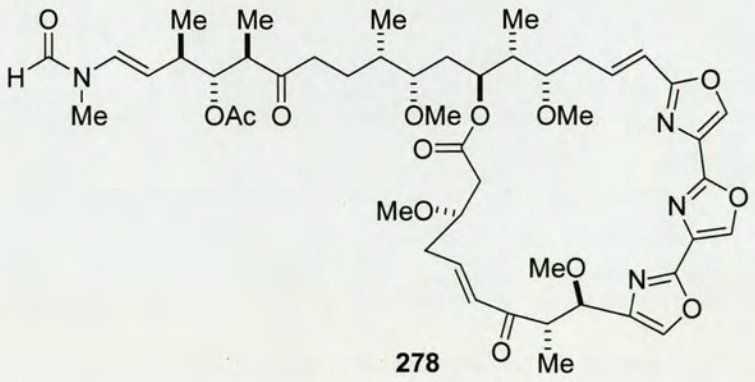


277

ulapualide A

Figure 28. Structure of ulapualide A.

The marine macrolide ulapualide A was isolated by Scheuer *et al.* in 1986 from the egg masses of nudibranch *Hexabranchus sanguineus* and differs only in the oxidation patterns and methyl substitutions when compared to mycalolide A (**278**), another tris-oxazole compound isolated in the 1980's.[201]

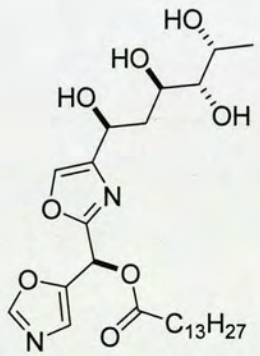


278

(-)-mycalolide A

Figure 29. Structure of (-)-mycalolide A.

Both structures share a highly interesting and synthetically challenging tris-oxazole fragment. Research in the Greaney group has yielded a successful route to this tris-oxazole fragment as described later in this chapter. Pattenden and co-workers have described a total synthesis of a diastereomer of the tris-oxazole containing natural product ulapualide A based on a straightforward condensation approach as discussed in chapter one. The oxazoles were formed using linear chain peptide precursors.[39,202]



279

bengazole A

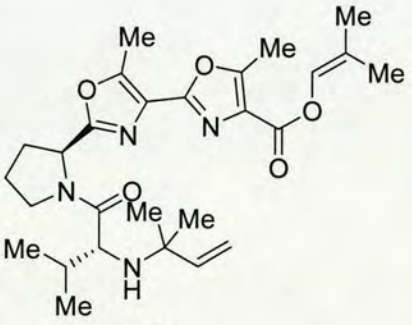
Figure 30. Structure of bengazole A.

Bengazole A (**279**), a bis-oxazole in which the oxazoles are not directly coupled to each other is shown in figure 30. Interestingly the molecule consists of a 5-

monosubstituted oxazole, which is an extremely rare feature, in addition to a typical 2,4-disubstituted oxazole. Bengazole A and its homologues were isolated from marine sponges of the genus *Jaspis*. Bengazole A exhibits strong antifungal activity against *Candida albicans* and fluconazole resistant *Candida* strains.[203-205] Molinski *et al.* were the first to report a total synthesis, followed by a more recent disclosure from the group of Shioiri.[206,207] Both of the total syntheses have been reviewed in detail.[39]

Directly linked 2,4-azole containing molecules such as ulapualide A have been found in nature and shown to exhibit interesting and potent biological activities.[208] Most of these oxazole containing natural products share a common framework, a bis- or trisoxazole.

Muscoride A (**280**) has weak antibiotic activities, it was isolated from the freshwater cyanobacterium *Nostocmuscorum* by the group of Sakakibara.[209] The total synthesis of this oxazole containing natural product has been reported by several groups. Firstly by Wipf and co-workers, followed by Pattenden *et al.* and most recently by the group of Ciufolini.[210-212]



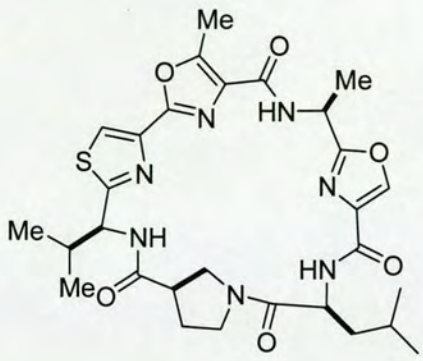
280

muscoride A

Figure 31. Structure of muscoride A.

Thiazole-thiazole linked natural products have also been isolated to date. Recently a few oxazole-thiazole 2,4-di- and polyazole natural products have followed those

reports in the literature. Namely telomestatin (thiazoline, not thiazole) – a strong telomerase inhibitor (Figure 4, Chapter 1), leucamide A (Figure 32, **281**), YM-216391 (**282**) – another cyclic peptide, and most recently mechercharmycin A and B.[213,214] (Figure 34 and 35, **283** and **284**)

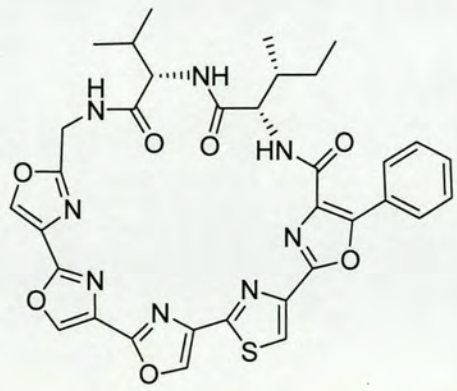


281

leucamide A

Figure 32. Leucamide A.

Leucamide A (**281**) is one of the more simple cyclic peptides described within this thesis as it only contains three heteroaromatic azole functionalities. It shows mild cytotoxic activity and was isolated from a marine sponge (*Leucetta microraphis*).[215] The group of Nan have published the total synthesis of this natural product based on a well-known valine-derived thiazole precursor previously described by Meyers and his co-workers.[216,217]



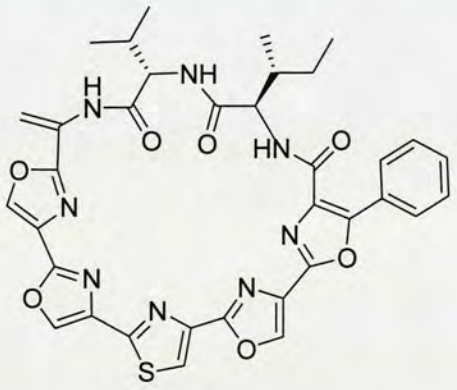
282

Figure 33. Structure of penta-azole YM-216391.

A further example - YM-216391 (**282**) - a poly-azole containing cyclic peptide with five directly connected 5-membered heterocycles was first discovered and isolated from *Streptomyces nobilis*.[218] This compound's structure is highly similar to the one of telomestatin, a potent anti-cancer molecule. Pattenden has described the only total synthesis of this interesting natural product in 2005 and more biological data is still required to determine the putative activities of this compound.[219]

Finally, the structure and properties of our target molecule are discussed. Mechercharmycin A (**283**) is a four-oxazole, one-thiazole containing cyclic peptide with a molecular weight of 708 da. Mechercharmycin B is the acyclic version of mechercharmycin A (**284**), both were isolated from the marine microorganism strain ES7-008.[208] Mechercharmycin B does not have any appreciable biological activity, mechercharmycin A however has been shown to have very strong cytotoxic activities (anti-tumour).[220]

The structure of mechercharmycin A is very distinct; it consists of a tri-peptide part which contains a centred L-valine residue with an D-*allo*-isoleucine to one side and an *exo*-double bond residue (from the elimination of the serine hydroxyl group) to the other.

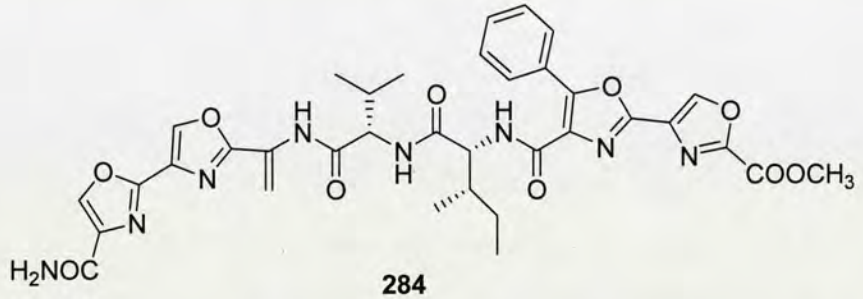


283

Figure 34. Structure of mechercharmycin A ($C_{35}H_{32}N_8O_7S$) (IB-01211).

Connected via the nitrogen of the isoleucine is a fully substituted oxazole bearing a phenyl group at its 5-position and another oxazole on its two-position. This second

oxazole itself has a vacant 5-position and is connected to the only thiazole in the molecule. Like the oxazoles it connects to, the thiazole has a free 5-position and connects to the fourth, directly linked, azole via its 2-position. This third oxazole (fourth azole clockwise) is coupled in the same fashion to the last oxazole. The cyclic ring structure is obtained when considering the bond between the 2-position of this very last oxazole and the internal carbon of the *exo*-double bond.



284

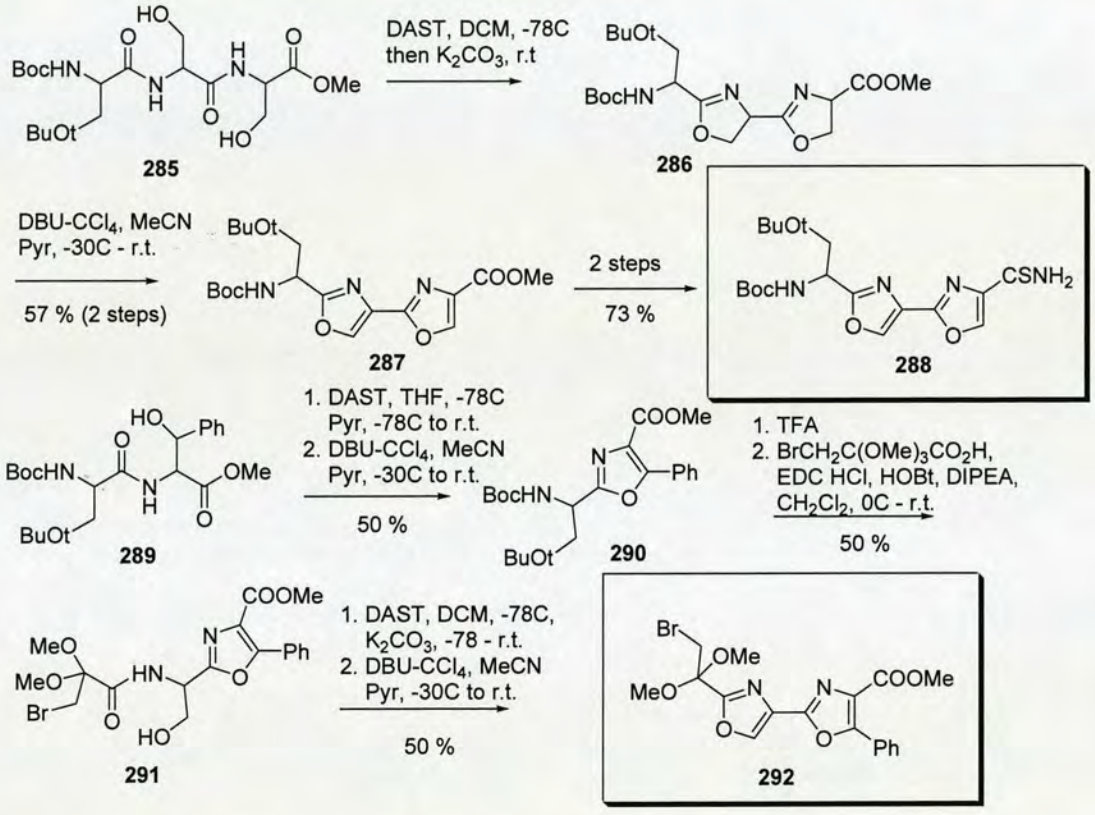
Figure 35. Structure of mechercharmycin B ($C_{35}H_{36}N_8O_{10}$), the linear congener of mechercharmycin A.

Biologically active natural products as lead compounds for the pharmaceutical industry and its drug discovery programs have a longstanding tradition. Many of today's drugs and pharmaceuticals have only been discovered or at least been optimised because a natural product provided an early insight into potential biological activities. The story of taxol (Paclitaxel) being a perfect example; taxol, a mitotic inhibitor used in cancer chemotherapy was discovered in 1967 and is still used, without any modification to its original structure, in today's anti-cancer treatments (e.g. breast cancer).[221]

3.1.2 Previous Total Synthesis of Mechercharmycin A

The total synthesis of mechercharmycin A has been achieved only once to this date. The research group of Alvarez has reported a synthetic route based on known peptide chemistry.[52] The key step in their synthesis is a Hantzsch macrocyclisation. As pictured in scheme 90, the synthetic sequence is commenced with a series of peptide

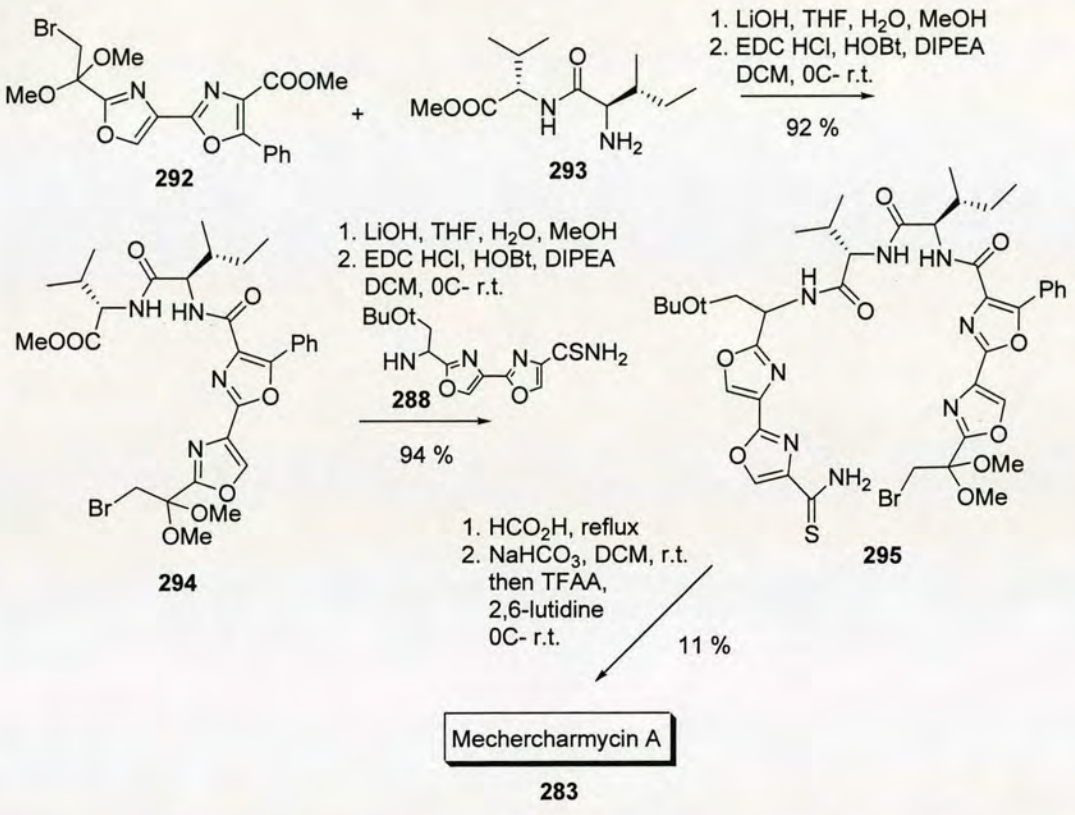
couplings. The Boc-protected tri-peptide **285** is cyclised to a bis-oxazoline fragment using the commercially available DAST reagent. The bis-oxazoline fragment **286** is then oxidized to the bis-oxazole structure **287** utilising a DBU-CCl_4 in pyridine procedure. Further functional group interconversion of the methyl-ester **287** to the thio-amide **288** in two steps (73 % over two steps) provided one of the three major fragments needed for the convergent synthesis of IB-01211.



Scheme 90. Synthesis of two key-fragments of mechercharymycin A.

The second azole containing fragment was synthesised in a similar fashion, starting with a peptide coupling to produce compound **289**. This di-peptide was then turned into highly functionalised oxazole **290** via the previously described sequence of DAST cyclisation followed by oxidation using DBU-CCl_4. The *tert.*butyl protected primary alcohol as well as the Boc-protected amine were simultaneously deprotected using TFA. The produced material was directly coupled via an EDC / HOBt

activated peptide coupling with $BrCH_2C(OMe)_2CO_2H$ to give compound **291**. Finally modification included a previously seen cyclisation via DAST at low temperature, followed by oxidation of the oxazoline fragment to bis-oxazole **292**. Further steps towards the total synthesis are presented in detail below (Scheme 91).



Scheme 91. Final steps towards the bio-mimetic synthesis of mechercharymycin A.

Bis-oxazole fragment **292** was coupled with prior synthesised di-peptide **293** (both unnatural amino-acids) using a standard peptide coupling procedure (EDC, HOBt, DCM, r.t.) to form compound **294** in excellent yield. A further peptide coupling between compound **294** and the bis-oxazole structure **288** was successfully employed and yielded the highly functionalised tetra-oxazole **295**. The penultimate step in this total synthesis was the deprotection of the primary alcohol using formic acid at reflux. Lastly, as mentioned earlier, the key step – a Hantzsch macrocyclisation – was described. An unsatisfactory yield for the last two steps was reported to be 11 %.

Given this final result, the total synthesis of mechercharmycin A (**283**) was accomplished in a respectable overall yield of just under 3.4 %.[52] Features of this approach are a repetitive peptide coupling, cyclisation and oxidation sequence as well as the Hantzsch macrocyclisation. This report is currently the only publication regarding the total synthesis of mechercharmycin A.

3.2 Aims of Project

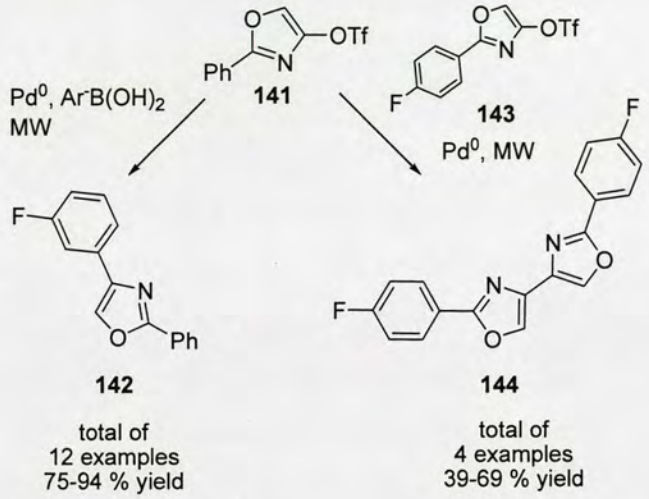
The aim of this project is to establish a strong, high yielding and convergent synthetic route for the total synthesis of the biologically active natural product mechercharmycin A. If at all possible, our previously developed methodologies should be used.[71,116] A non-peptidic approach is highly desired as this total synthesis should highlight the power of modern carbon-carbon bond forming reactions using transition metal catalysis. We envision a previously unseen direct arylation approach as the main highlight of this work, including a key direct-arylation macrocyclisation step to form the desired natural product. This synthesis should later allow the large scale synthesis of this target compound, possibly producing this molecule in 500 mg - 1 g. Further biological investigations of this compound are of great interest and could further highlight the biological effects of this cyclic peptide.

3.3 Previous Work in the Greaney Group

Research into oxazole-containing compounds has been a main topic in the Greaney group since its beginning. I am the second Ph.D. student fully dedicated to oxazole research. Prior to this work, a Ph.D. student (Dr. E. Ferrer-Flegeau) investigated oxazoles and their reactivities in detail. Highlighted below are some of the early findings of the Greaney group in the area of transition metal catalysed oxazole sp^2-sp^2 couplings.

The first report on oxazoles published by the Greaney group was a publication highlighting the functionalisation of the oxazole 2- and 4-position using a Suzuki coupling reaction. 2-Aryl-4-triflyloxazoles were shown to undergo rapid, MW-

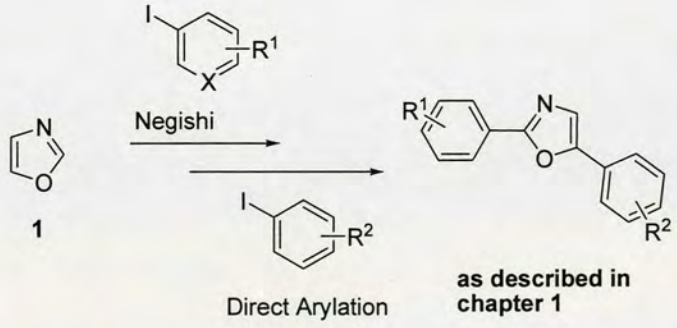
assisted couplings with a variety of boronic acids as described in chapter one of this thesis. This work formed the basis of oxazole-related research in the Greaney group.



Scheme 92. Ferrer-Flegeau and Greaney's work on Suzuki couplings using oxazoles. (as Scheme 47)

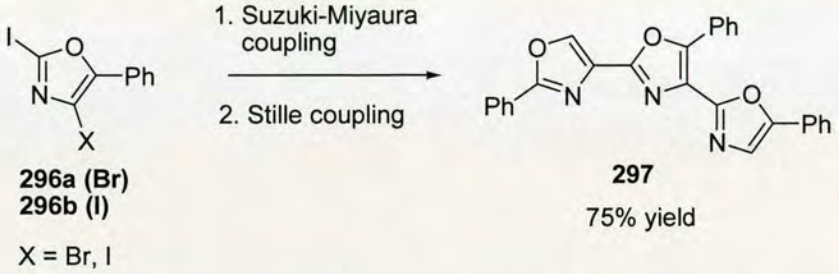
Continuous research into oxazole containing structures next revealed the first direct arylation of oxazoles on the 5- and 2-position by Ohnmacht *et al.* using on water conditions as described in the first chapter of this thesis.[182]

This work described the synthesis of two small oxazole containing natural products in combination with over 30 other directly arylated examples.



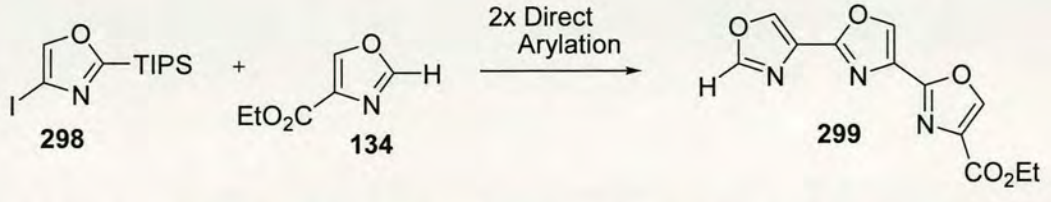
Scheme 93. Ohnmacht *et al.* reported the first 5- and 2-arylations of oxazoles on water.

Shortly after this report, Ferrer-Flegeau *et al.* published the work on the regioselective Suzuki-Miyaura cross-coupling of 2,4-dihalo oxazoles followed by Stille couplings. This work firstly describes the work in the Greaney group towards the synthesis of bis- and tris-oxazoles, a fragment seen in many poly-oxazole containing natural products such as hennoxazole A or ulapualide A, and of importance to the total synthesis of mechercharmycin A.[222]



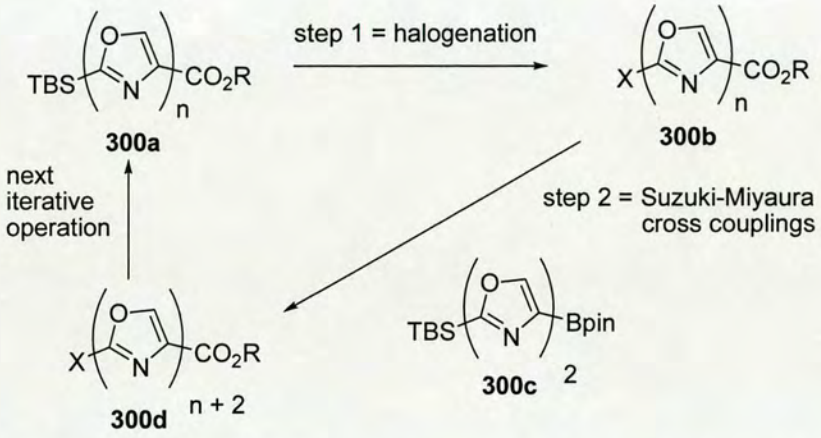
Scheme 94. Ferrer-Flegeau *et al.* reported the formation of a tris-oxazole fragment.[222]

The last and most recent publication investigating oxazole reactivities authored by Greaney and Ferrer-Flegeau is highlighted below. This interesting publication further describes the synthetic efforts towards poly-oxazoles, this time investigating the effects and scope of direct arylation methodology. The authors describe the stepwise elongation of 4-substituted oxazole **134** to poly-oxazole **299** via a palladium catalysed method based on Hermann-Beller's palladacycle. It is this paper and the results shown in scheme 95 that formed the basis for the retrosynthetic route for the total synthesis of mechercharmycin A described within this chapter.



Scheme 95. Formation of tris-oxazoles via TM-catalysed direct arylation.[116]

The only literature precedent of poly-oxazoles (tris-oxazoles and higher oligo-oxazoles) coupled via a TM-catalysed methods other than the Greaney group's work to this date is the work of Inoue and co-workers.[223] Their 2007 communication provides a detailed look into an iterative two-step strategy for C2-C4' linked poly-oxazoles (**300d**) using the Suzuki-Miyaura reaction. Drawbacks of this approach are the need for excessive functionalisation of the precursors and the extremely linear approach.

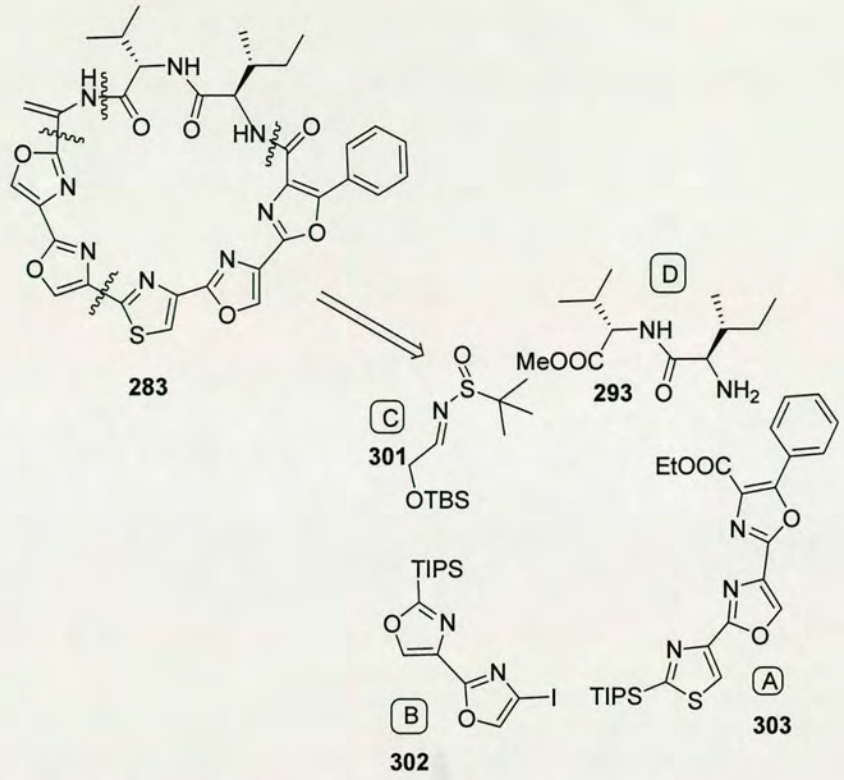


Scheme 96. Synthesis of bis-, tris-, tetrakis-, pentakis- and hexakis-oxazoles.[223]

3.4 Results and Discussion

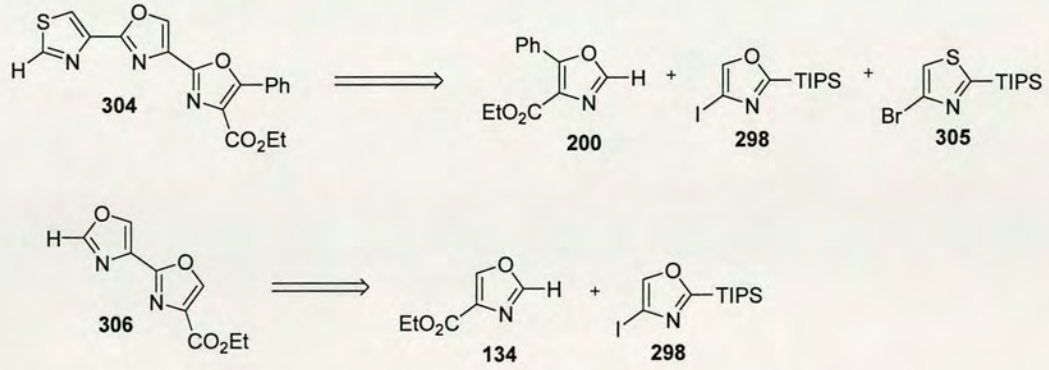
3.4.1 Retrosynthesis

Based on the above shown results obtained in the Greaney group over the last several years it was decided to disconnect the structure of mechercharmycin A in a highly convergent fashion. Retrosynthetic analysis provided four fragments. The analysis focused on either breaking a simple peptide bond or disconnecting using a site in the molecule where a sp^2-sp^2 cross coupling could later be utilised.



Scheme 97. Retrosynthetic analysis of mechercharmycin A.

The ability to synthesise 2,4-diiodo-oxazole (**309**) (scheme 101) has clearly influenced our decision to generate fragments A and B.[116] Both fragments will be generated using similar approaches. Scheme 98 shows in detail the further breakdown of fragments A and B into readily available (via synthesis, not commercially) molecules.



Scheme 98. Detailed retrosynthesis of fragments A and B.

Possible key-transformation in this total synthesis would be a direct arylation macrocyclisation, catalysed by a transition metal, possibly coordinating up to four of mechercharmycin A's nitrogens, which present themselves to the inside of the molecule. The authors postulate that this is possible, knowing that tris-oxazoles such as kabiramide C and halichondramide have the capacity to sequester and transport metal ions *in vivo* using the curve-linear array of the oxygen and nitrogen bearing ligand binding sites in their structures.[224] Further support is given by the existence of a coordinated sodium ion in the crystal structure of IB-01211.[52]

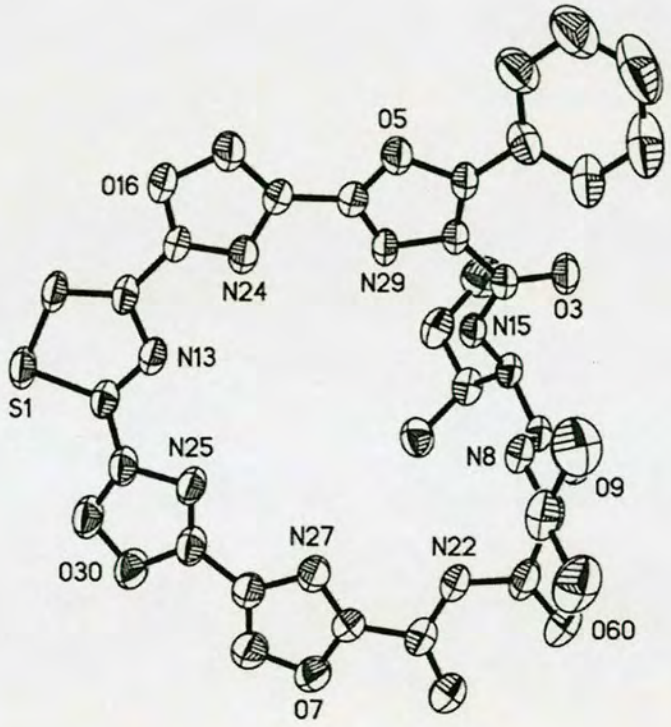


Figure 36. Top-down X-ray structural analysis of mechercharmycin A (**283**) (NaOMe removed from center).

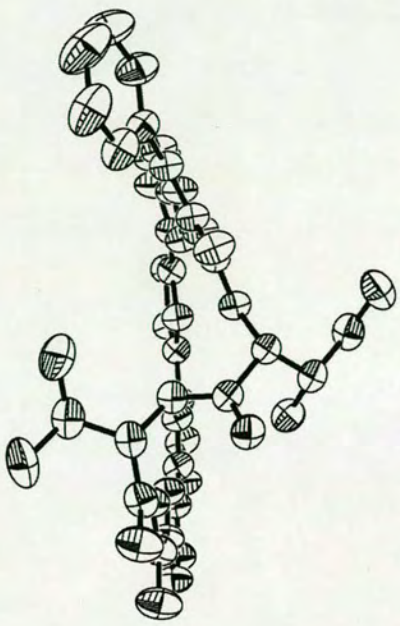
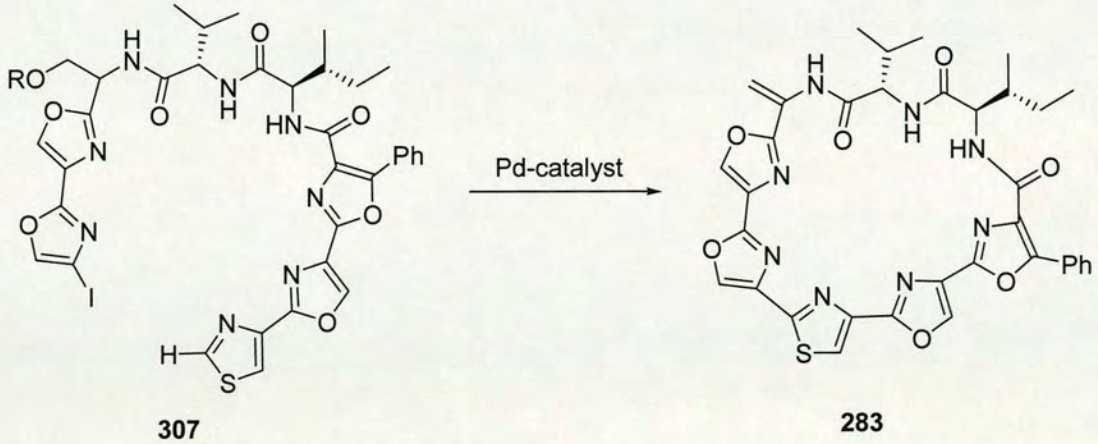


Figure 37. Side-view of mechercharmycin A (**283**) (NaOMe removed from center).

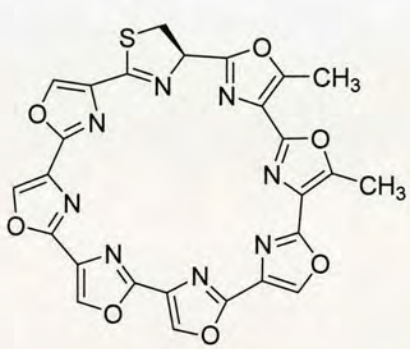
This is a very ambitious step, however, the authors believe that highly optimised conditions, including the correct dilution could make this reaction possible.



307 **283**

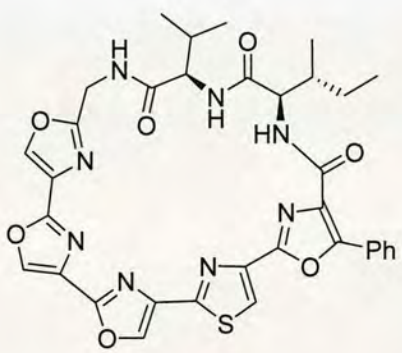
Scheme 99. TM-catalysed macrocyclisation to form cyclic peptide **283** using a direct arylation approach.

We decided to chose this novel and highly uncertain approach following close inspection of Professor Pattenden's work in this area. Pattenden was first to synthesise a tris-oxazole fragment and did so in a respectable 14 steps with an overall yield of 6 %.[225] The Pattenden group have published extensively on macrocyclisation reactions of poly-azole containing cyclic peptides.[226,227] Most of their work describes macrocyclisations using peptide bond formations in very undesirable yields, generally below or around the 40 % yield mark. It needs to be noted at this point that the yield quoted in the previous sentence is only obtained when one of the internal azoles is not yet cyclised to a five-membered ring. Pattenden and co-workers have investigated the macrocyclisation reactions of penta-azoles (all connected to each other and therefore completely flat) via peptide bond formation and have provided strong experimental evidence that the macrocyclisation of such systems is not possible at all.[228] Due to the extreme similarity of our target compound to the compounds described in Pattenden's work we decided to opt for a different approach and accepted, that many years of detailed research in the Pattenden group would very likely also prove themselves correct and therefore not of use for our target compound. In addition, we were keen to show the strength of direct arylation in a macrocyclisation step. To the best of our knowledge this has to date never been achieved.



44

Telomestatin

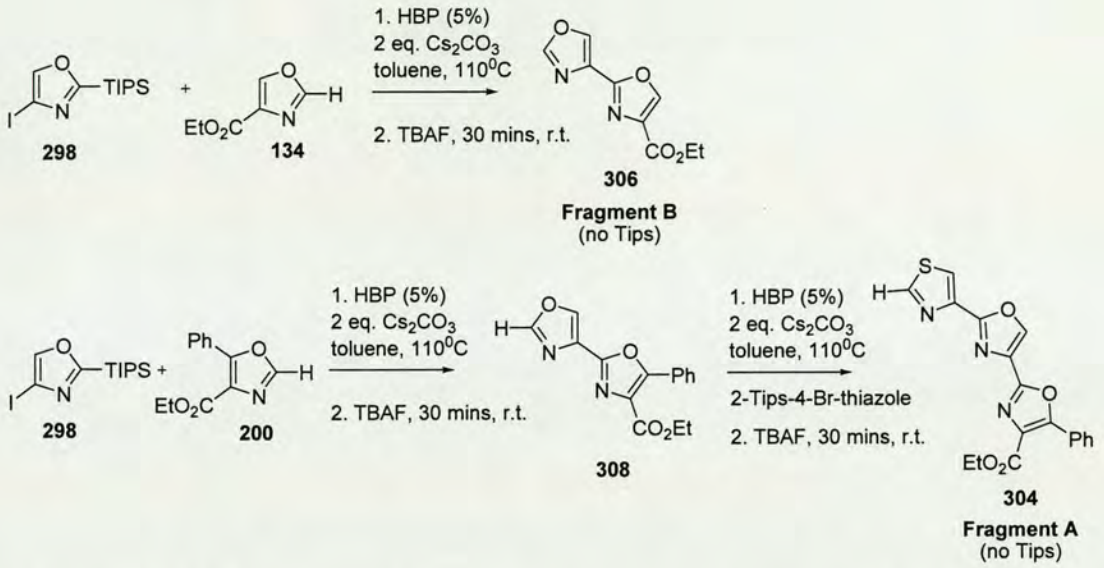


282

YM-216391

Figure 38. Compounds generated via peptide-bond macrocylisation in the Pattenden group.

3.4.2 Synthesis and Synthetic Steps

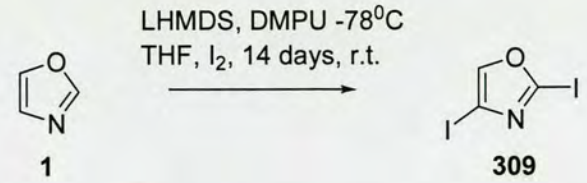


Scheme 100. Synthetic route for the generation of fragments A and B.

Scheme 100 shows the possible synthetic strategy for the synthesis of fragments A and B. Both fragments are generated in a similar fashion, using the previously published approach discovered by Ferrer-Flegeau and Greaney. Further manipulation of the precursor to fragment A with a halo-thiazole could prove effective.

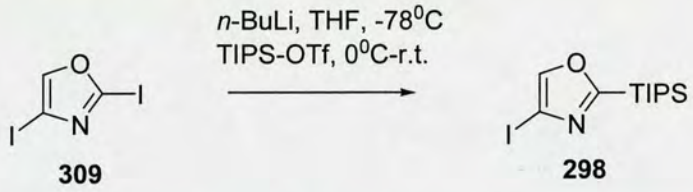
Synthesis of fragments C and D should be straightforward using known literature procedures.[50,229] The di-peptide fragment D is a known compound and has been described in the literature by Doi *et al.* on their way to generate telomestatin.[50] Fragment C can be synthesised in one step using Ellmann's chiral sulphinamide chemistry.[229,230] This procedure should provide easy access to fragment C and any analogs possibly required.

First synthetic efforts were directed to the generation of 2,4-diiodo-oxazole (**309**). Following the procedure of Ferrer-Flegeau *et al.*, compound **309** was formed in a reaction that required 14 days to complete. Isolated yields were generally in the range of 50 – 70 %. Optimisation of these rather slow reaction conditions was not attempted as the reaction proceeded well at the described temperature.



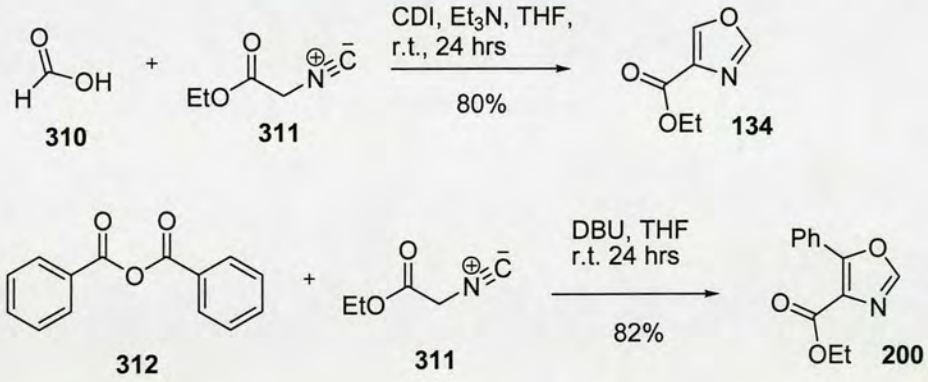
Scheme 101. Synthesis of 2-4-diiodo-oxazole.

Following the synthesis of compound **309**, 2-Tips-4-iodo-oxazole **298** was generated, once again following the previously developed method from the Greaney group. Isolated yields of this transformation ranged widely, from < 10% to around 70%, depending on the quality of starting materials and reagents. Absolutely dry solvents were necessary for this transformation to occur.



Scheme 102. Synthesis of 2-Tips-4-iodo-oxazole.

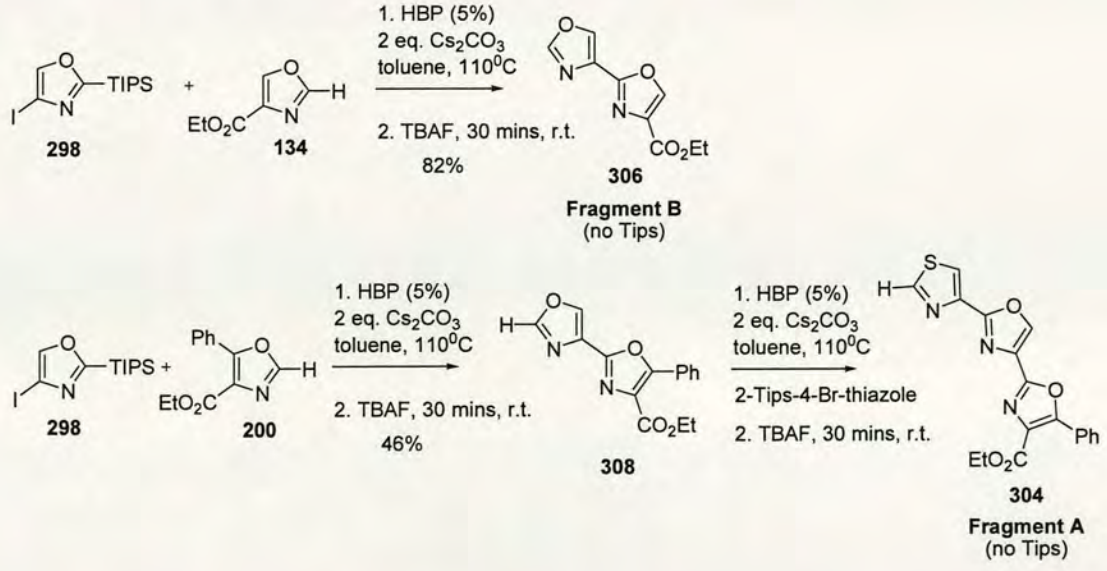
Following the successful synthesis of 2-Tips-4-iodo-oxazole (**298**), its coupling partners for the envisioned direct arylation were generated in excellent yields.



Scheme 103. One-step synthesis of oxazole precursors **134** and **200**.[142]

With both starting materials in hand, the direct arylation reaction to form bis-oxazoles **306** and **308** were attempted and shown to be a success. Compound **306** had previously been generated in the Greaney group, compound **308** however was a novel molecule. Both syntheses generated the target compounds in moderate to good yields. Compound **308** was isolated in a much lower yield due to the existence of the phenyl substituent on the 5-position of the oxazole, which clearly changes the electronic nature of the precursor. This decreased isolated yield proved to be true as this reaction was repeated several times, always yielding the final bis-oxazole **308** in a lower yield compared to the non-phenyl-substituted oxazole **306**.

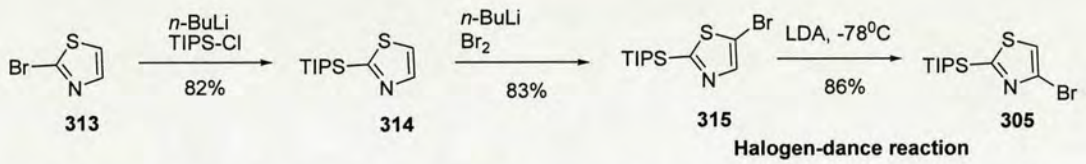
In order to further modify this bis-oxazole **308** we needed to remove the Tips-protecting group. This can be done in two separate ways. Firstly, compounds **306** and **308** can be isolated and then put into a room temperature solution of TBAF (1 equiv.) for 30 mins. Washing and extracting of that solution provides the deprotected bis-oxazoles in high yield. Secondly, the deprotection of compounds **306** and **308** can be achieved *in situ*; after the work-up stage (following the extraction) the organic phase containing either compound **306** or **308** is dried with $MgSO_4$ and filtered. The filtrate (compound still dissolved in DCM) is then put into a small Erlenmeyer flask and TBAF (1 equiv. of 1M solution in THF) is added. Similar to the first procedure the solution is stirred for 30 mins and then re-extracted to yield the final product in a combined yield (over two steps) of 82 % for **306** and 46 % for compound **308**.



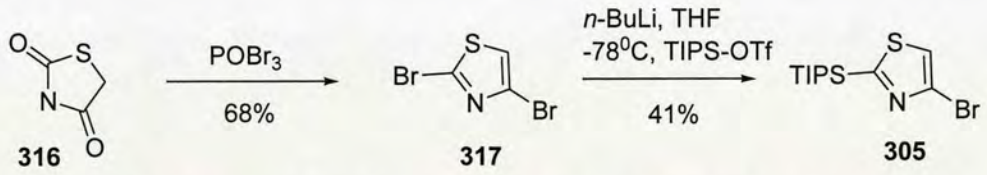
Scheme 104. Final steps of each cross coupling step is the removal of TIPS protecting group using TBAF. (as Scheme 100)

Deprotection of Tips-protected bis-oxazole **353** (see experimental) provided fragment B in excellent yields via a sequence of four synthetic steps. This compound was stored at room temperature until further modification was necessary.

Compound **308** needed further modification via another direct arylation step. The starting material needed for such a transformation was 2-Tips-4-bromo-thiazole (**305**). This compound has been described in the literature only once before.[231] This report provides a rather tedious synthesis of the title compound via three strong base reactions (2x *n*-BuLi, 1x LDA). We attempted a different approach which proved successful; however only low yields of 2-Tips-4-bromo-thiazole (**305**) were isolated.

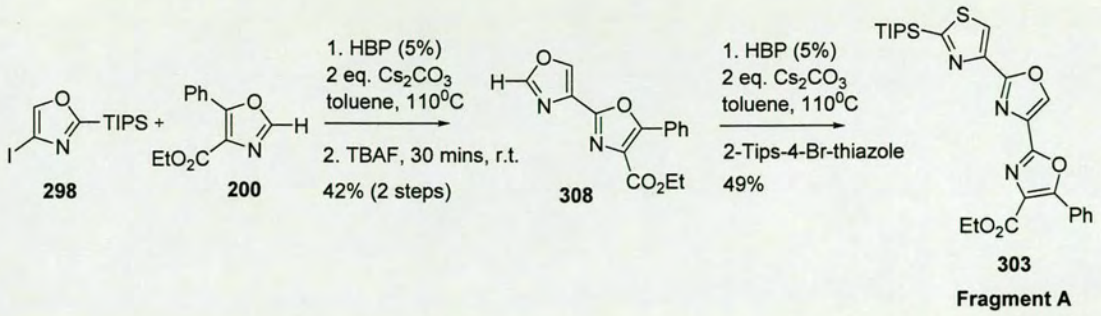


Scheme 105. Sole known synthetic procedure for the formation of **305**.[231]



Scheme 106. New synthetic approach to 2-Tips-4-bromo-oxazole.

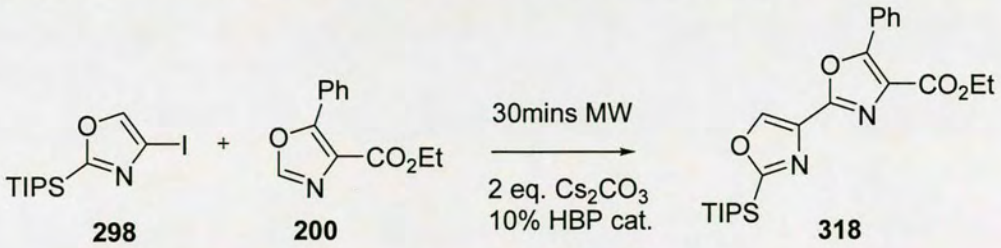
Having both starting materials in hand, a second direct arylation was attempted and proved successful in its first try. Bis-oxazole **308** was reacted with 2-Tips-4-bromo-oxazole **305** under the previously identified conditions using Hermann-Beller's palladacycle and Cs_2CO_3 as the base of choice at elevated temperature.



Scheme 107. Formation of protected tris-azole fragment A via direct arylation.

Once again *in situ* deprotection of the Tips-protecting group was achieved. A small optimisation study was launched to see if the yields of the coupling reaction (Table 19) could be increased using microwave technology.

Table 19. MW-accelerated screening of direct arylation conditions.



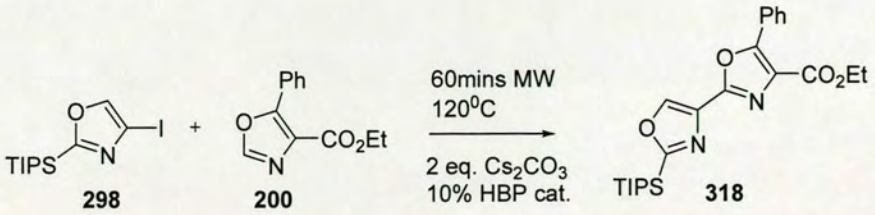
298 200 318

Solvent	Temperature (°C)	Result
Toluene	120	30% yield[a)]
Dioxane	120	24% yield[b)]
DMF	135	no product
THF	70	no product
NMP	150	no product
DMA	150	no product
Water	110	no product

a) 37% starting material recovered
b) 40% starting material recovered

Multiple temperatures were screened and changes in the amounts of reagents were investigated. No conditions to increase yields were identified.

Table 20. Follow-up screening based on the success of toluene and dioxane as solvents.



Catalyst (10%)	Solvent	Result
PEPPSI	Dioxane	no product
PEPPSI	Toluene	no product
Pd_2dba_3	Dioxane	no product
Pd_2dba_3	Toluene	no product
$Pd(dppf)Cl_2$	Dioxane	no product
$Pd(dppf)Cl_2$	Toluene	no product

Crystal growth of intermediate **308** was made possible when a solution of dichloromethane and diethyl ether was allowed to slowly evaporate over several days. X-ray crystal analysis of the generated needle-like crystals allowed the visualisation of this highly planar bis-oxazole.

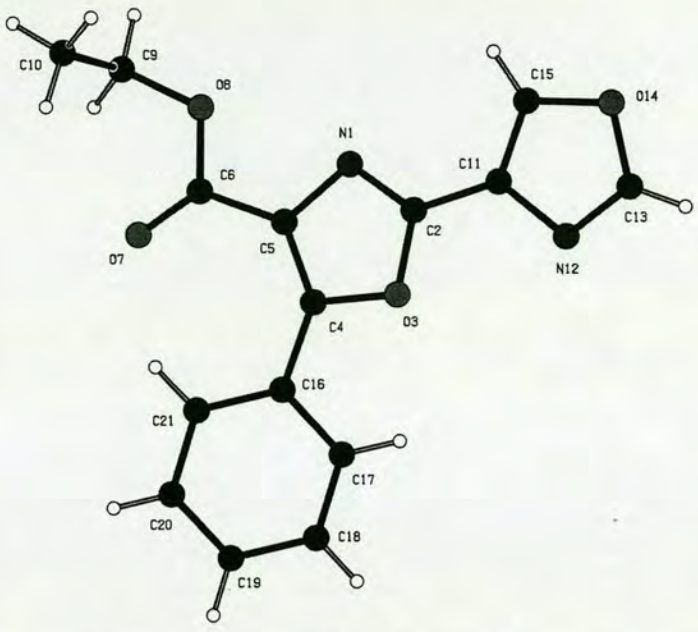
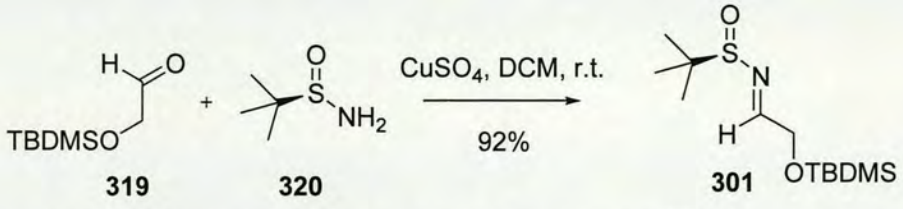


Figure 39. X-ray analysis of compound **308** after Tips-deprotection step.

Having fragment A and B in hand, attention was now turned to the synthesis of fragment C.

As mentioned earlier, Ellmann's sulphinamides should provide quick and easy access into a class of reactive imines. The choice of 'Ellmann imines' was not our initial choice. We envisioned a simple benzyl protecting group to be of use, which can then be removed via a mild hydrogenation reaction. Early work into the synthesis of compounds with the substructure **301** (in which the imine is a non-sulphinamide) quickly showed that these compounds are highly unstable. Following several weeks of dedicated research to find a set of conditions it was decided to abandon the benzyl protected imine and investigate more stable schiff bases. (Note: Ellmann's imine analogue **301** is stable at room temperature for several weeks under nitrogen)

Synthesis of compound **301** was straight forward yielding the imine in excellent yield.



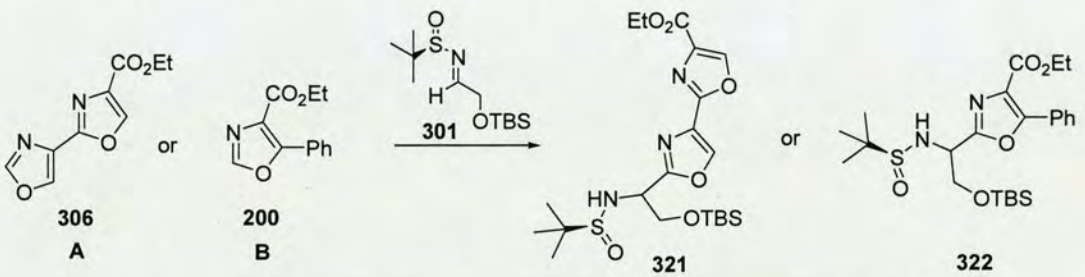
319 **320** **301**

Scheme 108. Synthetic route to generate fragment C.[229]

3.4.3 Connecting Fragments

Major problems occurred when trying to connect fragment B to fragment C. It was thought that a strong base, such as *n*-BuLi, could easily deprotonate (see ring opening mechanism of oxazoles at the 2-position) the oxazole and then attack the electrophilic carbon atom of the imine.

Table 21. Attempts to couple fragment B to fragment C.

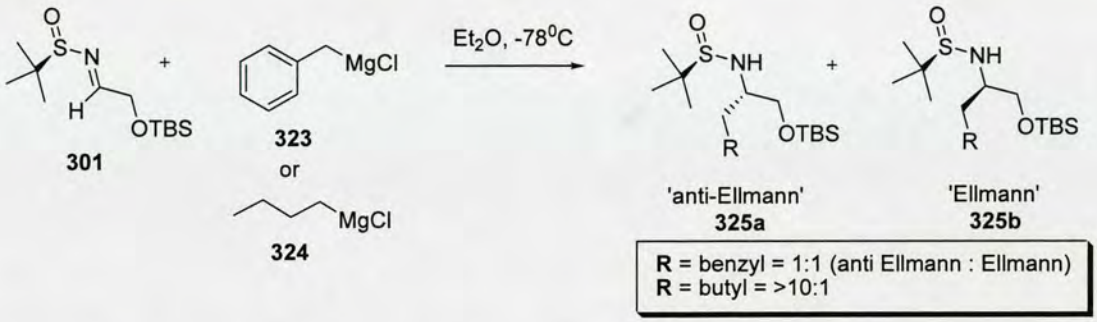


Starting Material	Base (1.1 eq.)	Result
A	*n*-BuLi	no addition
A	LHMDS	no addition
A	Cs_2CO_3	no addition
A	*i*PrMgCl	no addition
A	*i*PrMgCl/LiCl	no addition
B	*n*-BuLi	no addition
B	LHMDS	no addition
B	Cs_2CO_3	no addition
B	*i*PrMgCl	no addition
B	*i*PrMgCl/LiCl	no addition

In fact, deprotonation of the 2-position of oxazole is a trivial reaction and has been achieved many times throughout the work of this thesis. However, in this case the generated anion did not attack imine **301** in any way. Imine **301** quickly proved to be highly stable and unreactive towards the attack by the 2-position of oxazole.

Switching the base from *n*-BuLi to LHMDS did not increase the reactivity of the imine towards this reaction. Additionally, *i*PrMgCl was thought to possibly enhance

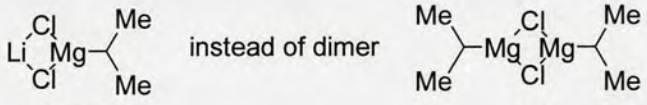
the rate of carbon-carbon bond formation in this transformation. The reason for this was a 2001 publication by Ellmann and colleagues in which they described the addition of Mg-based organometallics to imines.[232] Scheme 109 provides a detailed look at the conditions and the use of Grignard-type precursors for addition reactions onto imines.



301 323 or 324 325a 325b

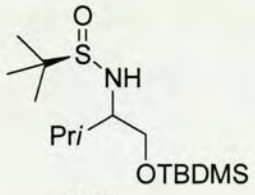
Scheme 109. Use of Ellmann's homochiral *tert.*-butylsulfinamide in addition reactions.

Several different methods were researched and attempted, one of them using LiCl as an additive to avoid any dimer formation of the Grignard reagent (Scheme 110).[233] None of the methods described provided any respectable amounts of the desired product on the LCMS. The only product visible on a regular basis was the addition product of *i*PrMgCl and the imine (Figure 40, **328**).



326 **327**

Scheme 110. LiCl additive to prevent dimer formation of the Grignard reagent.[233]

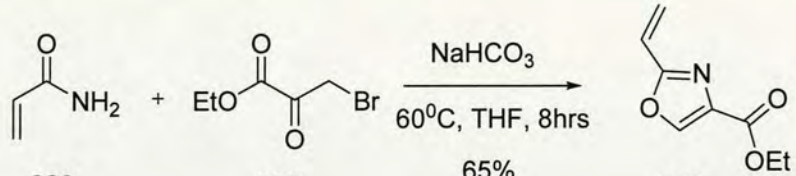


328

Figure 40. Major product identified by LCMS.

The reason for choosing Cs_2CO_3 as a base for the deprotonation of the 2-position of the above mentioned oxazole starting materials **306** and **200** was a paper by Sanchez and Zhuravlev in 2007. This publication was discussed in detail in the first chapter and highlights the ability of this base to generate the ring-opened form of oxazole, therefore generating a highly nucleophilic anion, which theoretically should attack the imine functionality at once.[144]

Following no real success in the preparation of a coupled molecule from fragment B and C, focus was turned away from the direct modification of the 2-position of oxazole via treatment with strong bases. This change of direction was supported by a brief chat with Prof. Ellmann at the BOSS conference in Belgium. Prof. Ellmann was already aware of the difficulties imposed by the ring opening mechanism of oxazoles when attempting to couple the 2-position of an oxazole with his sulphinamide analogues. A completely new approach was therefore drawn out and preparation of the starting materials got on its way (Scheme 111).



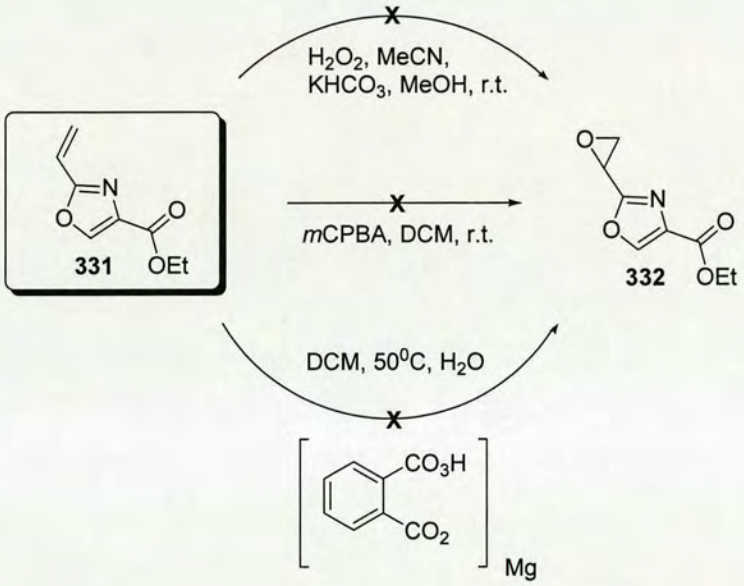
329 **330** **331**

Scheme 111. One-step synthesis of ethyl 2-vinyl-oxazole-4-carboxylate.[234]

The idea was to epoxidise the vinyl functionality of **331** using oxidising agents such as *m*CPBA or H_2O_2. It quickly turned out to be more difficult than expected with all

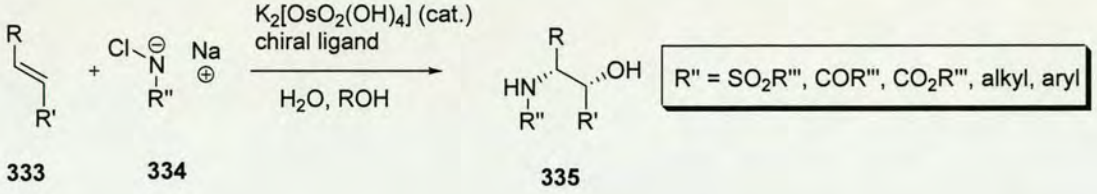
epoxidation attempts failing. Use of prolonged reaction times, excessive amounts of *m*CPBA as well as even small amounts of heating (behind blast shield at all times) at 40 °C did not provide any epoxidised material. Further reactions were attempted using reagents such as hydrogen peroxide or the rarely used peroxy-phthalate. All of these attempts did not provide any evidence of an epoxidation of the double bond.

Table 22. Epoxidation attempts with conditions using 2-vinyl-oxazole-4-carboxylate (**331**) - attempts to epoxidise ethyl 2-vinyl-oxazole-4-carboxylate **331** failed.



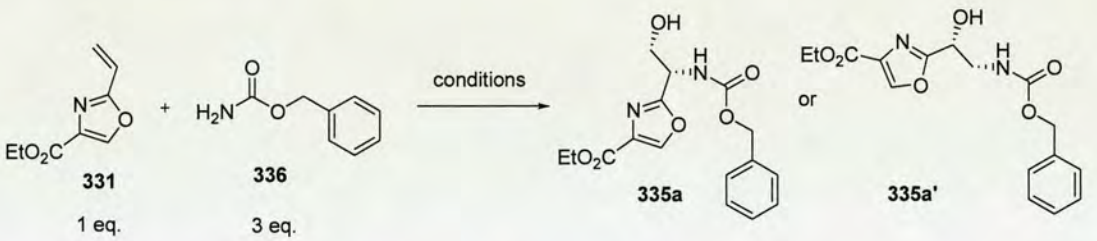
Oxidant / eqiv.	Time (h) / temp.	Result
*m*CPBA / 2	72 / r.t.	no epoxidation
*m*CPBA /1.2	1-24 / r.t.	no epoxidation
*m*CPBA / 6	3 / 40^{0}C	no epoxidation
*m*CPBA / 12	24 / r.t.	no epoxidation
H_2O_2 / 1.2	24 / r.t.	no epoxidation
H_2O_2 / 1.2	48 / r.t.	no epoxidation
peroxy-phtalate	2-48 / r.t to reflux	no epoxidation

Given these discouraging results, further investigations into the modification of this double bond were started. It was found that a Sharpless aminohydroxylation could be of use.[235] This reaction uses the vinyl-oxazole, $K_2OsO_2(OH)_4$ as well as $(DHQ)_2PHAL$ in combination with a carbamate, an aqueous solution of NaOH and MeCN. Hydantoin or hyposulfite can be used as the oxidant.



333 **334** **335**

Scheme 112. General reaction scheme for the *syn*-selective Sharpless aminohydroxylation.[236,237]



331 1 eq. **336** 3 eq. **335a** **335a'**

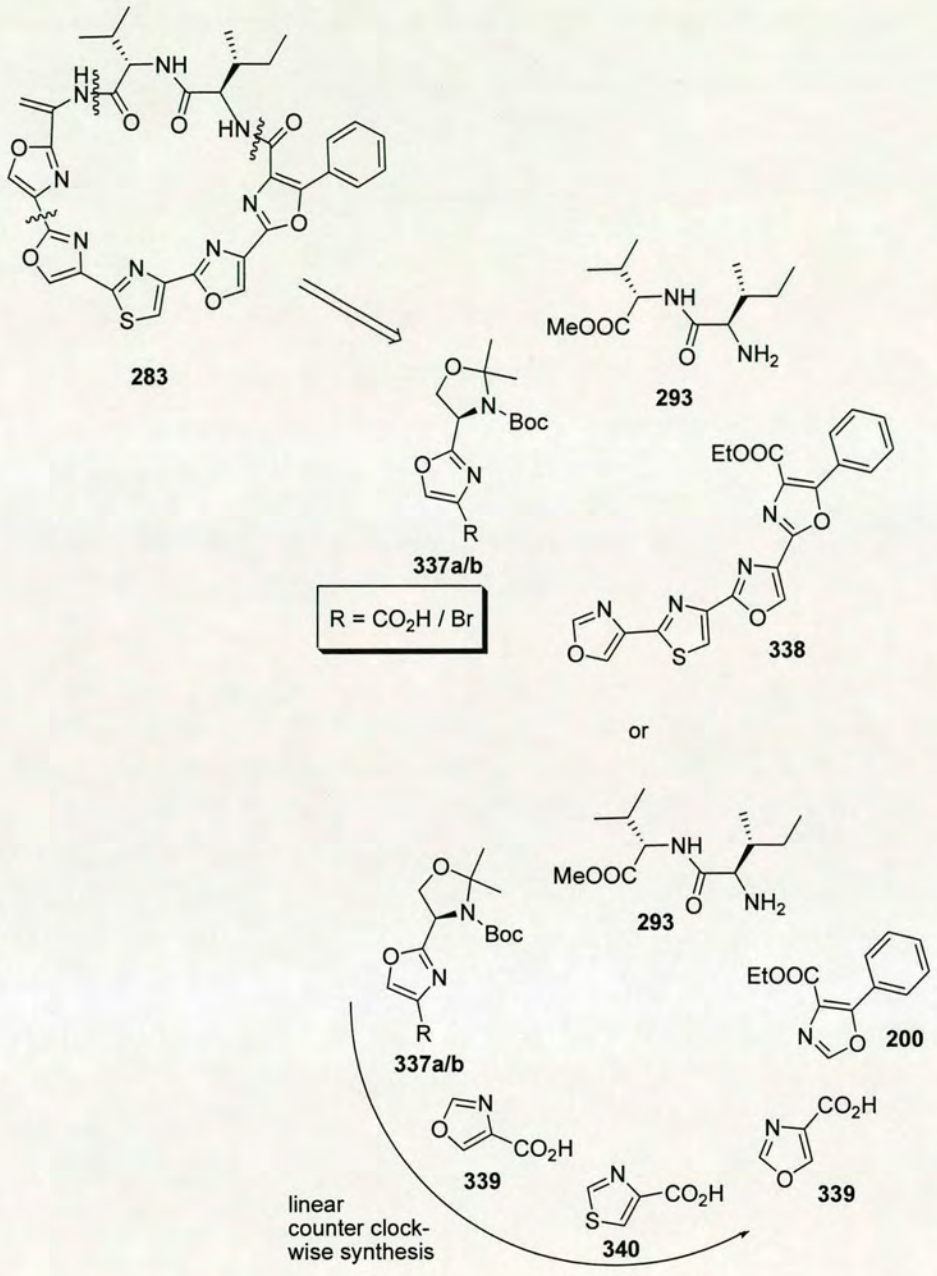
Conditions: $K_2OsO_2(OH)_4$ (4 mol%), NaOH (3 eq.), *t*OBuCl (3 eq.), H_2O, *n*-PrOH, $(DHQ)_2PHAL$ (5 mol %), 1,3-dichloro-5,5-dimethyl-hydantoin (3 eq.).

Scheme 113. Attempted oxyamination of 2-vinyl-oxazole-4-carboxylate **331** using Sharpless' conditions.

Several attempts to aminohydroxylate ethyl 2-vinyl-oxazole-4-carboxylate (**331**) were made but no isolated products were obtained. The product could be seen on the LCMS in 'small amounts' (amounts based only on UV traces), however TLC analysis and purification using silica did not produce any respectable amounts of product. After only a few attempts the decision was made to abandon this approach due to certain lack of selectivity in this transformation.

Following several weeks of investigations into the modification / connectivity of fragments B and C, a complete change of direction was envisioned. This decision was made due to the failure of the above described experiments as well as the general lack of reproducablity of the synthetic step from 2,4-diiodo-oxazole to 2-Tips-4-iodo-oxazole (Scheme 102).

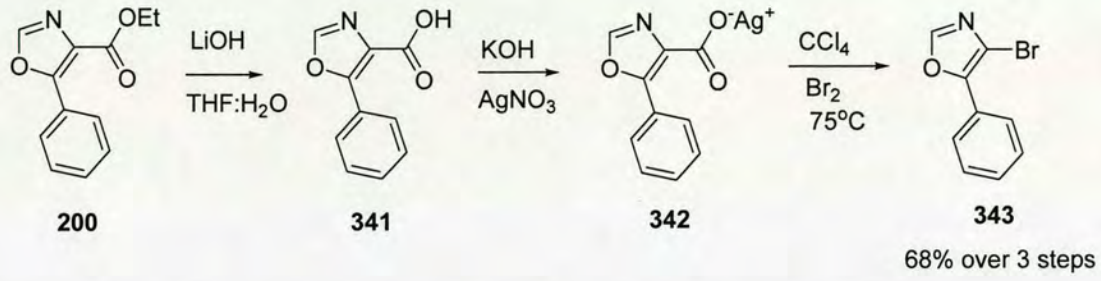
A new approach based on a classical transformation, the Hunsdiecker reaction, was designed. This approach would use a pre-formed (via peptide couplings) oxazole moiety, which has all the functionalities already installed at the required 2-position and would not require the use of any Tips-protecting groups. Scheme 114 shows the new approach to generate this highly useful substrate.



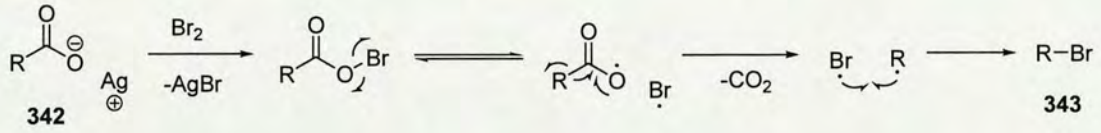
Scheme 114. Novel approach to the poly-azole moiety of mechercharmycin A.

Prior to the synthesis of oxazole precursor **337**, a trial reaction was run and showed highly promising results. 5-Phenyloxazole-4-carboxylic (**341**) acid was transformed into 4-bromo-5-phenyloxazole (**343**) in two steps in an overall isolated yield of 68 %. This is highly exciting as Barton and Zard stated: "The reaction is very sensitive to the presence of water and to the purity of the silver carboxylate but otherwise works

well with saturated aliphatic, and especially primary carboxylic acids."[238] No Hunsdiecker reaction on a heteroaromatic molecule was mentioned or highlighted in this report. The Hunsdiecker literature up to today only provides one example of an oxazole –carboxylic acid silver salt.[118]

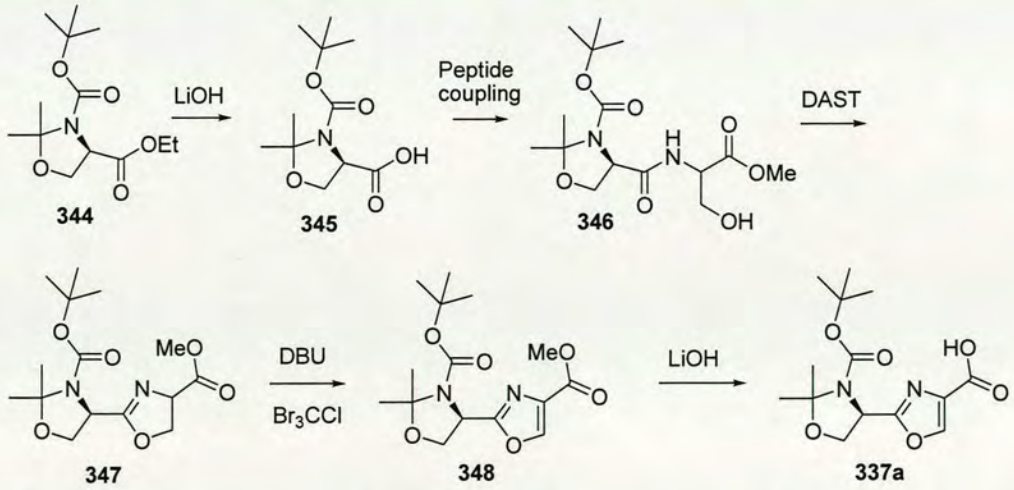


Scheme 115. Hunsdiecker test-reaction using 5-phenyloxazole-4-carboxylic acid.



Scheme 116. Mechanism of the Hunsdiecker (Borodin) reaction.

Given this success, a large scale peptide coupling, following the procedure in scheme 117, was initiated. Several steps later the highly functionalised oxazole **337a** was isolated and Hunsdiecker reactions could be commenced on the actual substrate.

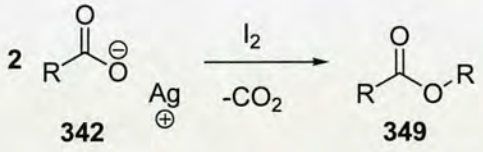


Scheme 117. Five-step synthesis of functionalised oxazole **337a**.

Commercially available **344** was firstly reacted in wet THF with LiOH to afford the acid **345**. Acid **345** was then further modified using a peptide coupling with L-Ser-OMe HCl to give structure **346**. DAST (Diamino-sulfur-trifluoride) then cyclised the di-peptide to the desired oxazoline intermediate **347**, which in turn was oxidised using the standard procedure of DBU / Br_3CCl. The freshly prepared oxazole was then once again put into wet THF and LiOH, providing the free acid **337a** for further modification. This synthetic sequence is known and has been reported in the literature.[239]

With the highly modified oxazole-carboxylic acid **337a** in hand, first attempts into the Hunsdiecker reaction were started. Ideally the acid should be converted into the silver salt using silver nitrate and then treatment with a bromine source would furnish the desired halogen on the 4-position of the oxazole compound (Scheme 116 – mechanism).

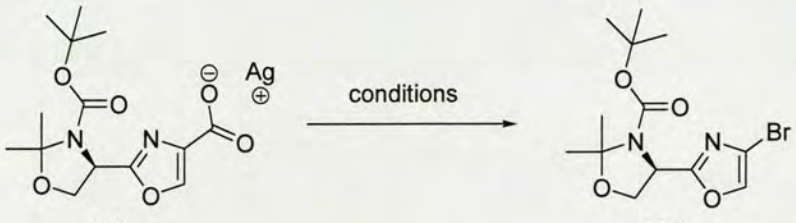
Given that the Hunsdiecker reaction is a classical reaction and has been discovered several decades ago, the reaction conditions shown in the literature are highly optimised and very specific.[240] For example, the use of iodine instead of bromine, known as the Simonini reaction, affords esters instead of the halogenated product.



Scheme 118. Simonini reaction.[241]

Based on a literature screening, two possible methods for the functional group transformation of the acid to the halide were identified. Br_2 or NBS were the most commonly used halide sources and have been shown to promote a vast amount of Hunsdiecker reactions in the past. It should be mentioned at this point that almost all of the Hunsdiecker and Borodin reaction literature transforms cinnamic acid analogues into the corresponding bromo-derivatives. Aware of this fact but given the success of our trial reaction using 5-phenyloxazole-4-carboxylic acid (**341**) it was decided to investigate the use of bromine first.

Table 23. Reaction conditions for the Hunsdiecker reaction of **350** with Br_2 and NBS.



350 **337b**

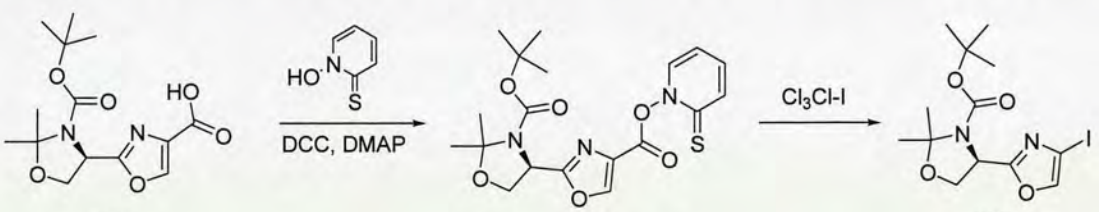
Time / Temp.	Solvent	Br-source	Result
2 / r.t.	CCl_4	Br_2 1.0 eq.	no conv.
8 / reflux	CCl_4	Br_2 excess	decomp.
2 / reflux	CCl_4	Br_2 1.0 eq.	decomp.
10min / reflux	CCl_4	Br_2 1.0 eq.	decomp.
2 / 50^{0}C	CCl_4	Br_2 1.0 eq.	decomp.
1.5 / reflux	CCl_4	NBS 1.1 eq.	decomp.
1.5 / r.t.	CCl_4	NBS 1.0 eq.	decomp.
2 / r.t.	CCl_4	NBS recry.	decomp.
2 / reflux	CCl_4	NBS recry.	decomp.

Transformation of acid **337a** into the silver salt **350** was spontaneous and provided the product in excellent yields as a light brown solid. Silver-salts of carboxylic acids are extremely light-sensitive and should be stored away from light sources at all times. It quickly became apparent however that the use of bromine would be a disadvantage due to the unreactive nature of our starting material under the selected conditions. Conditions were varied in such that the temperatures were increased from the standard ambient temperature up to 75 °C or 100 °C, amounts of bromine were varied from 1 to 3 equivalents, concentrations were changed as well as reaction times were constantly modified. None of the described conditions provided any encouraging conversions, new spots discovered on TLC plates were immediately

subjected to mass spectrometry analysis, to see if bromine isotopes could be found. None of the reactions involving bromine as the halogen source worked and investigations were changed to the other bromine-source, NBS.

Opposite to some of the previously described bromine reactions, most of the reactions run with NBS readily decomposed the starting material. Initial reactions were performed under refluxing carbon tetrachloride but were quickly changed to ambient temperature due to the constant decomposition of the starting material. Even at ambient temperature only small amounts of starting material (the acid, not the silver salt of course) could be re-isolated, with the remaining mass being unidentifiable polar spots. Any new spots apparent upon TLC analysis were once again analysed using mass spectrometry techniques to detect possible bromine isotopes. No bromine isotopes were discovered at any point in time.

Given a limited timeframe due to the apparent completion of the 3-year Ph.D. research period, a short investigation into the use of a Barton-decarboxylation was started. A handful of reactions were attempted but the Barton-ester **351** was not isolated in a successful manner, these reactions did not prove successful in my hands.



337a **351** Barton-ester **352**

Scheme 119. Proposed Barton-decarboxylation sequence.

3.5 Summary

The above chapter describes the design and subsequent retrosynthetic analysis of the total synthesis of the biologically active natural product mechercharmycin A, also found under the name of IB-01211. Further, four key fragments have been identified. Three of the four key fragments (A, B and C) have been successfully synthesised with the fourth fragment (D) being a di-peptide already known in the current

literature. Direct arylation methodologies previously discovered in the Greaney group were used to generate complex bis- and tris-azole fragments. Further, a novel approach for the generation of 2-Tips-4-Br-thiazole is described, which reduces the synthetic steps from the current three to a useful two steps.

All attempts to couple fragment B and fragment C have been shown to be unsuccessful, promoting a complete change in the retrosynthetic approach. Finally, investigations into the direct transformation of an aromatic carboxylic acid via its silver-salt using a classical Hunsdiecker reaction proved only successful with the test-substrate.

3.6 Conclusions and Future Work

Prior to the discovery of a decarboxylative coupling of oxazoles (by Dr. Zhang, post-doc 2010, Greaney group) the conclusion of this chapter would have highlighted the need for further investigations into the Barton-decarboxylation reaction using Barton's ester. Given our recent discovery of decarboxylative direct arylation, focus and future work now changed towards the development of a broadly applicable methodology. Several high yielding examples of this extremely interesting coupling have been isolated and progress has already been made to use this methodology towards the total synthesis of mechercharmycin A.

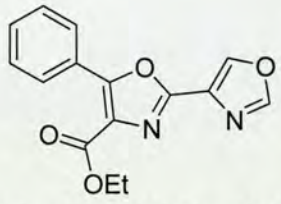
3.7 Experimental

General

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brüker dpx360 (360 MHz), Brüker dpx250 (250MHz) as well as a Brüker ava800 (800 MHz) instruments. Melting point measurements were obtained from a Gallenkamp melting point apparatus and are uncorrected. Electrospray high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finnigan MAT 900 XLT double focusing mass spectrometer. The data is recorded as the

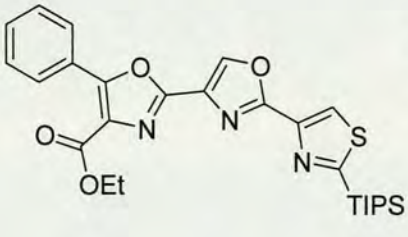
ionisation method followed by the calculated and measured masses. TLC was performed on Merck $60F_{254}$ silica plates and visualized by UV light. The compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. Distilled water was used in reactions carried out in water as the solvent.

Ethyl 2-(oxazol-4-yl)-5-phenyloxazole-4-carboxylate (308)



Bis-oxazole **318** (0.060 g, 0.136 mmol, 1 equiv.), was dissolved in DCM (2 ml) in a round bottom flask. To the solution, TBAF 1.6 M (1.02 ml, 0.164 mmol, 1.2 equiv.) was added via syringe at ambient temperature. After 25 minutes, 10 ml of DCM and 20 ml of deionised water were added and the two phases were separated via extraction. The aqueous phase was washed with DCM (2x 10 ml) and the combined organic layers were dried with $MgSO_4$. Filtration, followed by evaporation of the solvent afforded the crude product. Column chromatography in hexane : EtOAc (1:1) afforded the product in 82 % yield (32 mg) as an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.12-8.10 (m, 2H), 8.02 (s, 1H), 7.50-7.44 (m, 3H), 4.47-4.41 (q, 2H, *J*=7.1 Hz), 1.42-1.38 (t, 3H, *J*= 7.1Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.4 (quat), 154.8 (quat), 152.5 (quat), 151.3 (CH), 139.1 (CH), 130.0 (CH), 129.2 (quat), 128.2 (2x CH), 127.9 (2x CH), 127.5 (quat), 126.1 (quat), 115.7 (quat), 61.1 (CH_2), 13.8 (CH_3). **HRMS** (EI) m/z calcd for $C_{15}H_{12}N_2O_4$ 285.0875; found 285.0878.

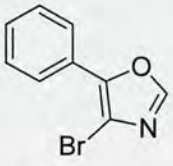
Ethyl 2-(2-(2-(triisopropylsilyl)thiazol-4-yl)oxazol-4-yl)-5-phenyloxazole-4-carboxylate (303)



Compound **308** (55 mg, 0.196 mmol, 1.0 equiv.) was added to a vial containing Cs_2CO_3 (128 mg, 0.392 mmol, 2 equiv.), Hermann-Beller-palladacycle (10 % mol) and 2-Tips-4-bromo-thiazole (**305**) (69 mg, 0.216 mmol, 1.1 equiv.). To

the mixture was added dry toluene (3 ml) via syringe. The solution was stirred at 140 °C for 4 hrs in a Biotage microwave reactor (Initiator). Work up included removal of the MW-vial lid, addition of DCM (10 ml) as well as deionised water (10 ml), followed by phase separation and washing of the aqueous phase with DCM (2x 5 ml). The combined organic layers were dried using $MgSO_4$. Evaporation of the solvents at reduced pressure provided the crude product, which was purified using silica chromatography (hexane : EtOAc 9:1) to then afford the pure product in 46 % yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.44 (s, 1H), 8.20-8.15 (m, 2H), 7.55-7.49 (m, 3H), 4.50-4.44 (q, 2H, *J*= 7.1 Hz), 1.57-1.48 (sept, 3H), 1.46-1.42 (t, 3H, *J*=7.1 Hz), 1.21-1.19 (d, 18H, *J*= 7.5 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6 (quat), 162.0 (quat), 158.8 (quat), 155.4 (quat), 153.4 (quat), 145.9 (quat), 139.3 (CH), 130.8 (quat), 130.5 (CH), 128.8 (CH), 128.4 (CH), 128.1 (quat), 126.7 (quat), 124.3 (CH), 61.6 (CH_2), 18.5 (CH_3), 14.3 (CH_3), 11.7 (CH). **HRMS** (EI) m/z calcd for $C_{27}H_{33}N_3O_4SSi$ 524.2039; found 524.2029.

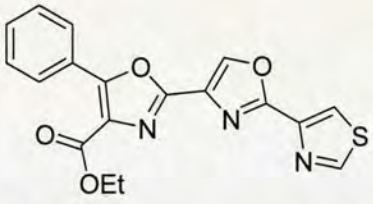
4-Bromo-5-phenyl oxazole (343)



To a solution of 5-phenyl-4-carboxylic acid (250 mg, 1.32 mmol) and potassium hydroxide (72 mg, 1.5 mmol) in water (10 ml) was added a solution of silver nitrate (105 mg, 1.5 mmol) in water (10 ml). The reaction mixture was stirred at room temperature for 2 hrs and filtered. The salt was washed with water, air dried, and finally dried under vacuum at 60 °C overnight. The salt was suspended in carbon tetrachloride (10 ml) under a nitrogen atmosphere, and bromine (224 mg, 1.4 mmol) was added drop wise. The reaction mixture was heated under 75 °C for 1.5 hrs and then filtered. The filtrate was partitioned between 2 M sodium hydroxide (10 ml) and dichloromethane (25 ml) and the aqueous layer was further extracted with dichloromethane (2 x 25 ml). The combined organics were washed with brine (25 ml), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (hexane : ether, 9:1) and gave compound **343** in an overall yield of 68 %. **^{1}H NMR** (250 MHz, $CDCl_3$) δ 7.95-7.91 (2H, m), 7.87 (s, 1H), 7.46-7.39 (3H, m). **^{13}C NMR** (63 MHz, $CDCl_3$) δ

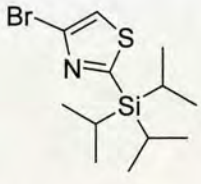
149.6 (CH), 146.6 (quat), 129.4 (CH), 129.0 (2xCH), 126.6 (quat), 125.5 (2xCH), 110.8 (quat). **HRMS** (EI) m/z calcd for C_9H_6BrNO 222.9627, found 222.9626.

Ethyl 5-phenyl-2-(2-thiazol-4-yl)oxazol-4-yl)oxazole-4-carboxylate (304)



Synthesised according and analogues to the previously described Tips-deprotection method using TBAF. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.48 (s, 1H), 8.44 (s, 1H), 8.20-8.15 (m, 2H), 7.55-7.49 (m, 3H), 4.50-4.44 (q, 2H, *J*= 7.1 Hz), 1.57-1.48 (sept, 3H), 1.46-1.42 (t, 3H, *J*=7.1 Hz), 1.21-1.19 (d, 18H, *J*= 7.5 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6 (quat), 162.0 (quat), 158.8 (quat), 155.4 (quat), 150.0 (CH), 145.9 (quat), 139.3 (CH), 130.8 (quat), 130.5 (CH), 128.8 (CH), 128.4 (CH), 128.1 (quat), 126.7 (quat), 124.3 (CH), 61.6 (CH_2), 18.5 (CH_3), 14.3 (CH_3), 11.7 (CH). **HRMS** (EI) m/z calcd for $C_{18}H_{14}N_3O_4S$ 368.0705, found 368.0713.

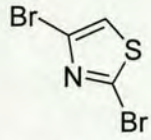
4-Bromo-2-(triisopropylsilyl)thiazole (305)



Dry THF (25 ml) was added to a flask containing 2,4-dibromo thiazole (1.0 g, 4.12 mmol, 1.0 equiv.) at room temperature under nitrogen atmosphere. The solution was cooled to –78 °C using a dry ice / acetone bath and then *n*-BuLi 1.6 M / hexane (2.77 ml, 1.1 equiv.) was added drop wise via syringe. The solution was stirred at that temperature for another 10 minutes, then allowed to go to 0 °C at which the Tips-OTf (1.16 ml, 1.05 equiv.) was added quickly but drop wise. The solution was allowed to reach room temperature and left stirring for 20 – 40 minutes. Water (50 ml) was added to quench the reaction as well as diethyl ether (50 ml). The two phases were separated and the aqueous phase was washed with ether (25 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Silica-gel column chromatography using hexane : EtOAc (9 : 1) afforded the final compound **305** as a colourless oil in 41 % (527

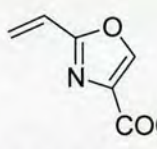
mg). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 1.47 (sept, 3H, *J*= 7.4 Hz), 1.11 (d, 18H, *J*= 7.4 Hz). **HRMS** (EI) m/z calcd for $C_{12}H_{23}BrNSSi$ 320.0498; found 320.0503.

2,4-Dibromo-thiazole (317)



This is a known compound. A mixture of thiazolidine-2,4-dione (3.40 g, 29.0 mmol) and phosphorus oxybromide (25 g, 87.0 mmol, 3.0 equiv.) was heated at 110 °C. After 3 hrs, the reaction mixture was cooled to room temperature and cautiously hydrolysed with crushed ice (also put flask in ice-bath). The resulting mixture was extracted with ether (2 x 200 ml) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (pentane : ether 99 : 1) to afford the final compound in 61 % yield (4.3 g). **^{13}C NMR** (63 MHz, $CDCl_3$) δ 136.2 (quat), 124.1 (quat), 120.8 (CH).

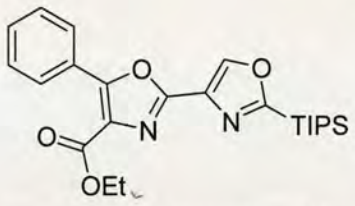
Ethyl 2-vinyloxazole-4-carboxylate (331)



This is a known compound. $NaHCO_3$ (11.4 g, 136 mmol) in powder form was added to a dry flask equipped with a stirrer. This was followed by the addition of acryl amide (2.41 g, 33.9 mmol) as well as THF (130 ml). The suspension was stirred and a first batch of bromo-pyruvate (5.2 ml, 37 mmol) was added via syringe. The flask was heated to 60 °C for 15 hrs and then another batch of bromo-pyruvate (3.0 ml, 21.0 mmol) was added. This mixture was stirred at 60 °C for another 8 hrs after which the flask was cooled to room temperature and the solid particles filtered. The filtrate was solidified by removing solvents under reduced pressure. The obtained solid was redissolved at 0 °C in THF (15 ml). Further, still at 0 °C, TFAA (15 ml) was added and the mixture was then allowed to reach room temperature over night. After 20 hrs, $NaHCO_3$ was added to neutralise the pH. (Caution!). Further, EtOAc (300 ml) and water (300 ml) were added and the two phases were separated. The organic phase was dried with $MgSO_4$ and filtered. The crude product was purified over silica using 3 : 1 (hexane : EtOAc) to afford the pure product **331** in 59 % yield.[234] **^{1}H NMR** (400 MHz, $CDCl_3$)

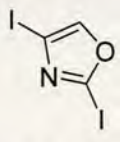
δ 8.20 (s, 1H), 6.74-6.67 (dd, 1H, *J*= 11.3, 17.7 Hz), 6.34-6.30 (d, 1H, *J*= 17.7 Hz), 5.79-5.66 (d, 1H, *J*= 11.3 Hz), 4.47-4.41 (q, 2H, *J*=7.1 Hz), 1.42-1.38 (t, 3H, *J*= 7.1Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.4 (quat), 161.2 (quat), 143.4 (CH), 134.4 (quat), 124.0 (CH), 122.7 (CH), 61.3 (CH_2), 14.4 (CH_3).

Ethyl 2-(2-(triisopropylsilyl)oxazol-4-yl)-5-phenyloxazole-4-carboxylate (318)



Ethyl-5-phenyloxazole-4-carboxylate (31 mg, 0.177 mmol, 1.2 equiv.) was added to a vial containing 4-Iodo-2-triisopropylsilanyl-oxazole (50 mg, 0.142 mmol, 1.0 equiv.), Cs_2CO_3 (93 mg, 0.284 mmol, 2.0 equiv.) and Herrmann-Beller catalyst (0.007 g, 5 mol %). To this mixture was added dry toluene (2 ml) via syringe. The suspension was stirred at 115 °C in the sealed tube for 24 hours. DCM (5 ml) and deionised water (10 ml) were added the following day and the aqueous phase was washed once with DCM (5 ml). The combined organic layers were dried using $MgSO_4$, filtered and the solvent removed using reduced pressure. The crude product was purified by silica gel chromatography using 9:1 (hexane : EtOAc) to give the bis-oxazole **318** in 56 % yield. Both starting materials were isolated during chromatography and combined accounted for the rest of the mass. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.12-8.10 (m, 2H), 7.51-7.44 (m, 3H), 4.49 (q, 2H, *J*= 7.1 Hz, 14.2 Hz), 1.51-1.39 (m, 6H), 1.16 (d, 18H, *J*= 27.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.5 (quat), 162.1 (quat), 155.0 (quat), 154.1 (quat), 142.0 (CH), 130.3 (CH), 129.7 (quat), 128.7 (2x CH), 128.3 (2x CH), 128.0 (quat), 126.9 (quat), 61.5 (CH_2), 18.2 (6x CH_3), 14.3 (3x CH), 10.8 (CH_3).

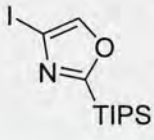
2,4-Diiodooxazole (309)



The compound was synthesised according to Vedejs' procedure with modifications. 1,3-Oxazole (1.00 ml, 14.900 mmol, 1 equiv.) was dissolved into a mixture of anhydrous THF (6.4 ml), anhydrous DMPU (5.2 mL), and cooled to -78 °C. LHMDS (32.80 ml, 1M in THF, 2.2 equiv.) was then added drop wise and stirred for 1 h. After this time, solid iodine (7.600 g, 29.800

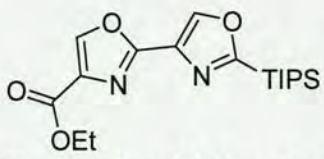
mmol, 2 equiv.) was added to the reaction mixture and stirred for an additional 30 min at -78 °C. The cooling bath was then removed and the reaction mixture was left to warm to rt and stirred for 14 days under a low positive pressure of N_2. The reaction mixture was then poured into a mixture of aqueous $Na_2S_2O_3$ (10%, 100 ml) and diethyl ether (100 ml). The organic layer was washed with brine (100 ml) and dried over $MgSO_4$. After filtration, the solvent was removed *in vacuo*. The residue was purified by flash chromatography (silica, hexanes / EtOAc, 9:1) to give the title compound **309** (3.701 g, 77 % yield) as a white solid. **Mp** 98-100 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 7.76 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 83.12 (quat), 101.56 (quat), 148.93 (CH). **HRMS** (ESI) calculated for $C_3H_1NOI_2$ 320.8142; found 320.8145.

4-Iodo-2-triisopropylsilanyl-oxazole (298)



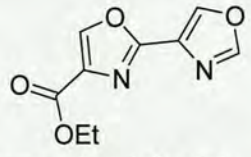
2,4-Diiodooxazole (500 mg, 1.558 mmol, 1 equiv.) was dissolved in dry THF (15 ml) and cooled to -78 °C. *n*-BuLi (1.17 ml, 1.870 mmol, 1.2 equiv.) was added drop wise to the cooled solution and the mixture was stirred for 20 min. Triisopropylsilyl trifluoromethanesulfonate (0.44 ml, 1.636 mmol, 1.05 equiv.) was then added slowly and the reaction mixture was stirred an additional 10 mins at -78 °C. At this point the cooling bath was removed and the reaction mixture was stirred for an additional 30 min at room temperature. The reaction mixture was quenched with water (50 ml) and diluted with diethyl ether (50 ml), the organic layer was washed with brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (hexanes / DCM, 4:1) yielded 487 mg (yield 89 %) of the desired product **298** as a light yellow oil. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.11 (18H, d, J = 7.2 Hz), 1.34-1.46 (3H, m), 7.79 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 10.90 (CH), 18.28 (CH_3), 81.83 (quat), 144.47 (CH), 171.00 (quat). **HRMS** (ESI) calculated for $C_9H_8N_2O_4$ 351.0510; found 351.0500. (Further purification can be achieved via Kugelrohr distillation (recommended for the direct couplings).

Ethyl 2-(2-(triisopropylsilyl)oxazole-4-yl)oxazole-4-carboxylate (353)



A 5 mL microwave type vial was charged with 50 mg of **298** (50 mg, 0.142 mmol, 1 equiv.), 4-Ethyl-oxazolecarboxylate **134** (25 mg, 0.177 mmol, 1.2 equiv.), Hermann's palladacycle (7 mg, 5 mol %), Cs_2CO_3 (93 mg, 0.284 mmol, 2 equiv.) and anhydrous toluene (1 ml). The vial was equipped with a magnetic stirrer bar, sealed and flushed with N_2. The vial and its contents were heated and stirred in a preheated oil bath at 110 °C for 16 hrs. After this time the vial was cooled to rt and the reaction mixture poured into a mixture of water (20 ml) and Et_2O (30 ml). The organic phase was separated and the aqueous layer was re-extracted twice with Et_2O. The organic layers were combined, dried over magnesium sulphate and after filtration the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, hexane / EtOAc, 9:1) to give the coupled product **353** as a yellow oil (42 mg, 81% yield). **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.18 (18H, d, J = 7.50 Hz), 1.38 (3H, t, J = 7.14 Hz), 1.40-1.49 (3H, m), 4.45 (2H, q, J = 7.14 Hz), 8.27 (1H, s), 8.52 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 10.91 (CH), 14.27 (CH_3), 18.28 (CH_3), 61.33 (CH_2), 129.63 (quat), 134.41 (quat), 141.98 (CH), 143.44 (CH), 156.42 (quat), 161.08 (quat), 170.52 (quat). **HRMS** (ESI) calculated for $C_{18}H_{28}N_2O_4Si$ 364.1813; found 364.1809.

Ethyl 2-(oxazol-4-yl)oxazole-4-carboxylate (306)

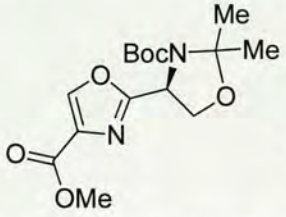


A 10 ml round bottom flask was charged with compound **353** (97 mg, 0.266 mmol, 1 equiv.), THF (5 ml) and aqueous TBAF (1 M, 0.41 ml, 0.410 mmol, 1.5 equiv). The reaction mixture was stirred for 25 min at rt, then diluted with water and extracted twice with DCM. The organic phase was washed with saturated aqueous NH_4Cl, brine (2x) and dried over magnesium sulphate, which after filtration and concentration *in vacuo* gave bis-oxazole **306** as a white solid (88 mg, 83% yield). **Mp** 117-119 °C. **^{1}H-NMR** (360 MHz, $CDCl_3$) δ 1.34 (3H, t, J = 7.1 Hz), 4.36 (2H, q, J = 7.1 Hz), 7.98 (1H, s), 8.26 (1H, s), 8.37 (1H, s). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ 14.17 (CH_3), 61.33 (CH_2), 129.48 (quat), 134.48 (quat), 139.65 (CH), 143.62 (CH), 151.78 (CH), 151.78 (CH),

155.33 (quat), 160.79 (quat). **HRMS** (ESI) calculated for $C_9H_8N_2O_4$ 208.0479; found 208.0480.

Alternatively, compound **306** can be prepared by re-diluting the dry crude from the previous step with 5 mL of THF, adding TBAF (0.14 ml, 1M in THF, 1.0 equiv) and stirring 25 min at rt. The mixture was then diluted with DCM and washed with NH_4Cl and brine (2x), dried over magnesium sulphate and after filtration the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica, hexane / EtOAc 1:1) to give the coupled product **306** as a white solid (21 mg, 71% yield, over 2 steps).

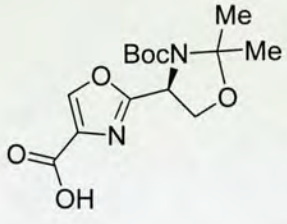
Ethyl 2-((S)-3-(tert-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)-oxazole-4-carboxylate (348)



To a solution of *N*-Boc-Ser-OH (13.0 g, 53.0 mmol) in CH_2Cl_2 (159 ml, 3.0 ml / mmol) was added H-Ser-OMe•HCl (9.1 g, 58.3 mmol), HOBt (8.6 g, 63.6 mmol) and DIEA (12.0 ml, 68.9 mmol) at room temperature, and the mixture was cooled to 0 °C. To the mixture was added EDCI•HCl (11.2 g, 58.3 mmol) at the same temperature and stirred at room temperature. After being stirred at the same temperature for 1 h, the mixture was poured into 1 M HCl at 0 °C. The aqueous layer was extracted twice with ethyl acetate. The organic layer was washed with 3 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The residue was used for the next reaction without further purification. To a solution of dipeptide in CH_2Cl_2 (159 ml, 3.0 ml / mmol) was added a solution of DAST (8.4 ml, 63.6 mmol) in CH_2Cl_2 at –78 °C under argon. After being stirred at the same temperature for 1 h, the mixture was poured into saturated aqueous $NaHCO_3$ at 0 °C. The aqueous layer was extracted twice with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. The residue was used for the next reaction without further purification. To a solution of oxazoline in CH_2Cl_2 (159 ml, 3.0 ml / mmol) was added DBU (24 ml, 159 mmol) at 0 °C under argon. To the mixture was slowly added $BrCCl_3$ (15.6 ml,

159 mmol) at the same temperature. After being stirred at room temperature for 3 hrs, the mixture was poured into 3 M HCl at 0 °C. The aqueous layer was extracted twice with ethyl acetate. The organic layer was washed with 3 M HCl, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on flash silica gel with 20% ethyl acetate in hexane to afford **348** (11.5 g, 35.5 mmol, 67% over 3 steps) as a yellow powder. The obtained NMR spectra matched the literature values. **^{1}H NMR** (400 MHz, DMSO-*d*6, 80°C) δ 8.71 (1H, s), 5.08 (1H, dd, J = 2.89 Hz, 6.76 Hz), 4.27 (1H, dd, J = 6.76 Hz, 9.42 Hz), 4.02 (1H, dd, J = 2.89 Hz, 9.42 Hz), 3.81 (3H, s), 1.63 (3H, s), 1.52 (3H, s), 1.31 (9H, bs).

2-((S)-3-(tert-butoxycarbonyl)-2,2-dimethyloxazoline-4-yl)-oxazole-4-carboxylic acid (337a)



To a solution of methyl ester **348** (6.0 g, 18.4 mmol) in MeOH (37 ml, 2.0 ml / mmol), THF (37 ml, 2.0 ml / mmol) and H_2O (9.2 ml, 0.5 ml / mmol) was added LiOH • H_2O (1.04 g, 25.0 mmol) at 0 °C. After being stirred at the same temperature for 3 hrs, the mixture was acidified with 3 M HCl at 0 °C. The aqueous layer was extracted twice with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. The residue was recrystalised with hexane / CH_2Cl_2 to afford **337a** (5.5 g, 17.5 mmol, 95 %) as a white powder. The obtained NMR spectra matched the literature values. **^{1}H NMR** (400 MHz, DMSO-*d*6, 80 °C) δ 8.59 (1H, s), 5.07 (1H, dd, J = 3.38 Hz, 6.76 Hz), 4.26 (1H, dd, J = 6.76 Hz, 9.18 Hz), 4.01 (1H, dd, J = 3.38 Hz, 9.18 Hz), 1.63 (3H, s), 1.52 (3H, s), 1.31 (9H, bs).

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3.9 Appendix

3.9.1 Publications

Direct arylations on water: synthesis of 2,5-disubstituted oxazoles balsoxin and texaline†‡

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An efficient two-step palladium catalysed synthesis of 2,5-disubstituted oxazoles is reported.

The functionalisation of heteroaromatic compounds by transition metal (TM) catalysed C–C bond formation complements classic condensation chemistry as a strategy for polyfunctional heteroaromatic synthesis.[1] Whereas classic heterocyclic synthesis frequently involves the preparation of appropriately substituted acyclic precursors which undergo cyclocondensation as a final step, TM-catalysed cross couplings offer the possibility of taking the parent, commercially available heteroarenes and selectively functionalising the C–H bonds around the heteroarene nucleus. The two approaches are illustrated in Scheme 1 for a 2,5-disubstituted azole synthesis. Whilst the condensation route is generally reliable and built upon many years of literature precedent, the preparation of the appropriately substituted precursor **1** is necessarily multi-step and the subsequent condensation is usually carried out under forcing conditions. The TM-catalysed approach offers significant advantages of speed and synthetic expediency in comparison, along with the potential for mild C–C bond forming reaction conditions.

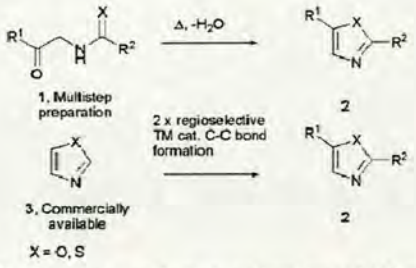
Importantly, the cross-coupling route enables the introduction of diversity at a late stage, rather than the early stage mandated by the condensation approach, a strategic advantage[2] in the type of intensive analog synthesis required by contemporary medicinal and agrochemical chemistry.

The TM-catalysed approach becomes even more attractive if direct arylation can be incorporated as a C–C bond forming reaction.[3] Here, the stoichiometric metallation required for classic cross-couplings such as the Suzuki–Miyaura, Stille and Negishi reactions is dispensed with, in favour of direct C–H bond functionalisation.[4] We now report the preparation of assorted 2,5-diaryloxazoles using TM-catalysed chemistry: Negishi coupling at the 2-position using a stoichiometric zincate followed by direct arylation at the 5-position under mild 'on water' conditions. The oxazole heteroarene structure has widespread application in medicinal, agrochemical, natural products and materials chemistry.[5]

Taking commercially available oxazole as our starting point, we functionalised the 2-position using a Negishi cross-coupling protocol developed by Reeder and co-workers.[6] Following lithiation with *n*-BuLi at −78 °C, solid $ZnCl_2$ is added to form the zincate, which subsequently undergoes Pd-catalysed coupling with aryl iodides at 60 °C. The procedure proved very effective for the preparation of the four 2-arylated oxazoles **6a–d**, **6b** having been exemplified in Reeder's work and **6a, c, d** being newly prepared using this method. With these substrates in hand, we turned our attention to the direct arylation of the oxazole 5-position. We have recently developed an effective on water[7] method for the direct arylation of heteroarenes;[8] high yields of arylated products are produced under far milder conditions than those typically employed in literature heteroarene arylations.

We were pleased to observe that the on water direct arylation is effective across a wide range of aryl iodides (Table 1), with yields being good to excellent for the 2-substituted oxazoles **6a–c**. The scope of aryl iodide covers electron rich (entries 5 and 6), electron poor (entries 3, 4, 7 and 9), sterically hindered (entries 2 and 10) as well as aryl iodides which contain additional functional handles for further elaboration such as aryl halide (entries 7 and 8) and acyl (entry 9). The process was poorly effective for pyridyl iodides,[9] producing very slow reactions with low yields of the oxazoyl pyridines (30–36%), with homocoupling of the oxazole being the dominant side-reaction.[10]

The average yield across the 30 examples in Table 1 was 85%, illustrating the power of the direct arylation method for the rapid assembly of functionalised heteroarenes. This is the first study of oxazole arylation that examines substrate range;



Scheme 1 Heteroarene synthesis *via* condensation and TM-catalysed methods.

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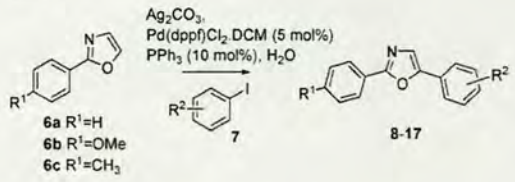
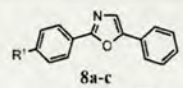
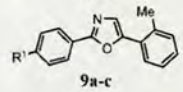
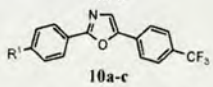
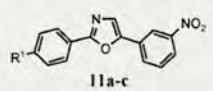
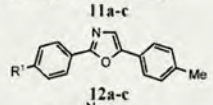
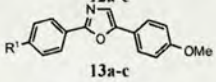
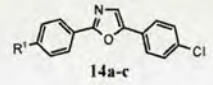
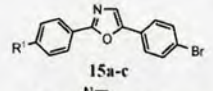
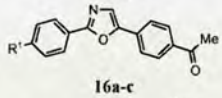
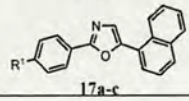
[b] *Global Discovery Chemistry, Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex, UK RH12 5AB*
† CCDC 671459. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b719466h
‡ Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds. See DOI: 10.1039/b719466h

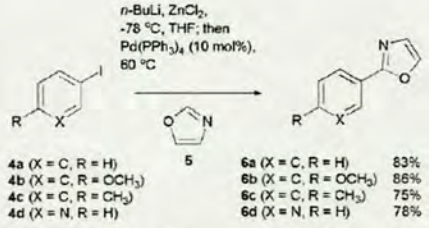
Table 1



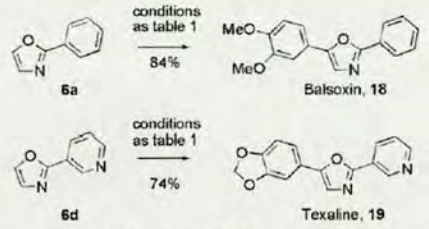
Entry	Products	Yield (%)
1	 8a-c	92 83 92
2	 9a-c	83 98 90
3	 10a-c	80 98 90
4	 11a-c	84 85 80
5	 12a-c	75 84 97
6	 13a-c	76 89 79
7	 14a-c	90 87 92
8	 15a-c	68 83 70
9	 16a-c	86 89 93
10	 17a-c	85 76 81

previous arylations of the oxazole 5-position having been confined to individual substrates and uniformly taking place at elevated temperatures.[11] Preliminary results suggest that the on water arylation will be effective for the acidic azole 2-position; treatment of 5-phenyloxazole with *p*-chloroiodobenzene afforded the 2,5-diaryloxazole product in a good 71% yield.[9]

Having established the method for the 2-step synthesis of 2,5-diaryloxazoles, we applied the chemistry to the rapid construction of two oxazole natural products. Balsoxin and



Scheme 2 2-Aryloxazole synthesis *via* Negishi cross-coupling.



Scheme 3 Synthesis of balsoxin and texaline.

texaline are 2,5-diaryloxazoles isolated from *Amyris* species of plant in the Caribbean,[12,13] with texaline reported to have antimycobacterial activity against *Mycobacterium tuberculosis, M. avium* and *M. kansasii*.[14]

The aforementioned Negishi coupling of aryl iodides with oxazole introduced the requisite 2-aryl substituent. A direct arylation at the 5-position with the electron rich aryl iodides 3,4-dimethoxyiodobenzene and 3,4-methylenedioxyiodobenzene afforded balsoxin, **18**, and texaline, **19**, respectively, in good yield (Scheme 3). The power of the direct arylation approach can be appreciated in comparison to literature preparations of these two natural products. Hodgetts and Kershaw synthesised balsoxin in 7 steps, 40% overall yield in a Suzuki–Miyaura approach, starting from ethyl 2-amino oxazole carboxylate,[15] whilst Copp and co-workers synthesised texaline in 6 steps, 4% overall yield using a condensation approach.[16]

In conclusion, we have developed a mild direct arylation method for the synthesis of 2,5-disubstituted oxazoles and applied it to the two-step assembly of balsoxin and texaline.

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ORGANIC LETTERS

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Direct Arylations of 2*H*-Indazoles On Water

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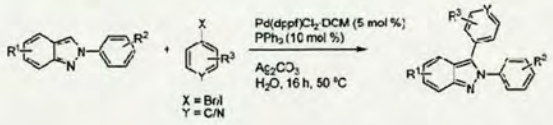
ABSTRACT



The efficient palladium-catalyzed synthesis of a range of substituted 2*H*-indazoles via C−H arylation is reported. Reactions are performed on water and provide a direct and mild route toward 2,3-diaryl indazoles of widespread biological significance.

Direct arylation is a powerful approach to the synthesis of functionalized arenes that offers an alternative to conventional cross-coupling methods.[1,2] The direct manipulation of C−H bonds in catalytic C−C or C−X bond formation avoids the preparation and use of stoichiometric organometallics, conferring the strategic benefit of streamlined, operationally simple synthesis with reduced byproduct formation.

A feature of current direct arylation methodology is the high reaction temperatures required to effect C−C bond formation, with relatively few systems being reported to date that proceed below 100 °C.[3] The development of new systems that function at milder temperatures will significantly enhance the scope and functional group tolerance of direct arylation as a general method of sp^2 C−C bond formation. We are addressing this issue through the development of direct arylation chemistry that works on water.[4] We have found that on water conditions, where substrate and catalyst system form a heterogeneous mixture in pure water, can be extremely effective for high yielding direct arylations under mild conditions.[5] We now wish to report our results on the application of on water arylation to the indazole substrate.

Although rare in nature, the indazole heterocycle has vast application in medicinal chemistry, particularly in the field of kinase inhibition.[6] Direct arylation at the C3 position would significantly simplify synthetic routes to this important class of heteroarene. Catalytic direct arylation of indazoles has received little attention, a single elegant study from Lautens on the synthesis of annulated 2*H*-indazoles via intramolecular direct arylation being the only extant report in the literature.[7]

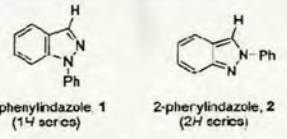


Figure 1. 1*H* and 2*H* indazoles.

We began by examining the regioisomeric 1- and 2-phenylindazoles as substrates (Figure 1). The C3 position is known to be markedly less reactive toward substitution in the 1*H*-series, and this was manifested in our direct arylation studies, with 1 undergoing no arylation on water under the mild conditions we were looking to develop. 2-Phenylindazole,[5] by contrast, proved an excellent substrate, undergoing clean on water

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(1) Recent reviews (a) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464 (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115.

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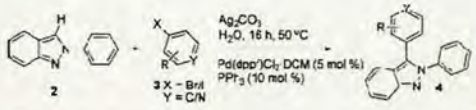
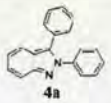
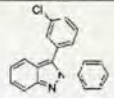
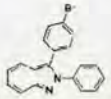
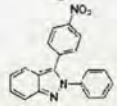
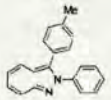
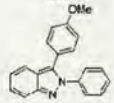
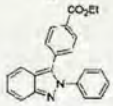
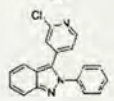
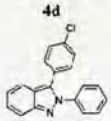
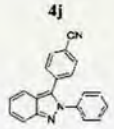
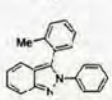
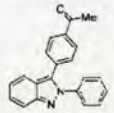
arylation with a variety of aryl halides at just 50 °C on water. A catalyst system of $Pd(dppf)Cl_2/PPh_3$ or $Pd(dppb)Cl_2/PPh_3$ in the presence of an equivalent of Ag_2CO_3 produced good to excellent yields of 2,3-diarylindazoles on water. The reaction was generally effective for both aryl iodides and bromides, an advance over our previous on water studies of azole heterocycles which were restricted to aryl iodides (Table 1).

Functional group tolerance was good, with halo (entries 2, 5, and 7), electron withdrawing (entries 4, 8, 11, and 12), and electron donating (entries 3, 6, and 9) groups being tolerated at both para and meta positions. A single ortho-functionalized aryl iodide was productive, but in a diminished 49% yield (entry 6). Heterocyclic 2-chloro-4-iodopyridine produced functionalized indazole **4j** in 95% yield, featuring the highly versatile 2-chloropyridine functionality for further manipulation (entry 10).

In practical terms the reactions were very simple to run and purify—a feature of on water chemistry. The catalyst system and substrates were premixed prior to the addition of water, with good mixing being crucial for successful arylation. While this was easily achieved for solid reactants (entries 2, 3, 4, and 8−10), care needed to be taken for reactions involving liquid aryl halides to prevent the reagent from adhering to the walls of the flask and not being effectively incorporated into the heterogeneous reaction mixture.

Table 1. Palladium-Catalyzed Direct Arylation of 2-Phenylindazole[a]



entry	product	yield (%)	entry	product	yield (%)
1	 **4a**	76 (From ArI) 71 (From ArBr)	7	 **4g**	96 (ArBr)
2	 **4b**	80[b] (ArI)	8	 **4h**	86 (ArBr)
3	 **4c**	91 (ArI) 70 (ArBr)	9	 **4i**	87 (ArI)
4	 **4d**	77 (ArI) 74 (ArBr)	10	 **4j**	95 (ArI)
5	 **4e**	90 (ArI) 69 (ArBr)	11	 **4k**	85 (ArI)
6	 **4f**	49[b] (ArI)	12	 **4l**	81 (ArI)

[a] X-ray structure of product. [b] Reaction run at 60 °C. [c] Conditions: Ag_2CO_3 (1 equiv), PPh_3 (10 mol %), $Pd(dppf)Cl_2$·DCM (5 mol %), Aryl iodide (1.1 equiv), 2-phenylindazole (1 equiv), water, 50 °C, 16 h. Isolated yields after SiO_2 chromatography.

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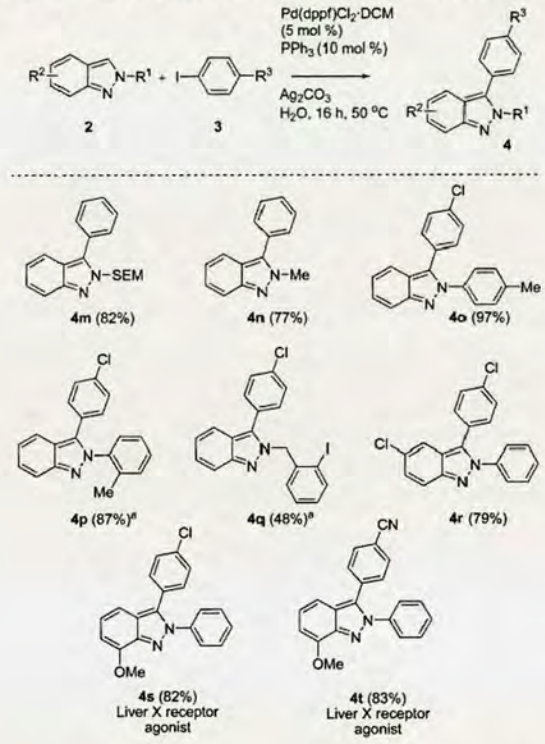
To fully establish the scope of the arylation we prepared a series of N2 substituted indazoles and subjected them to on water arylation (Table 2).

Table 2. Direct Arylation of Various 2*H*-Substituted Indazoles[b]



[a] Reaction run at 60 °C. [b] Conditions: Ag_2CO_3 (1 equiv), PPh_3 (10 mol %), Pd(dppf)Cl_2·DCM (5 mol %). Aryl iodide (1.1 equiv), 2-phenylindazole (1 equiv), water, 50 °C, 16 h. Isolated yields after SiO_2 chromatography.

The SEM protecting group proved stable to the arylation conditions, with the versatile 2-SEM protected indazole **4m** being formed in high yield. Alkyl-substituted indazoles were good substrates, as were 2-*p*- and *o*-tolylindazoles **4o** and **4p**. The 2-iodobenzylindazole starting material was prepared to examine the possibility of intramolecular cyclopentannulation via direct arylation. This intramolecular reaction proved ineffective under the conditions—when 4-chloroiodobenzene was added in a competition experiment the intermolecular arylation product was isolated in moderate yield. Functional handles could be incorporated into the indazole ring with the 5-chloro- and 7-methoxyindazole compounds being excellent substrates. Indazoles **4s** and **4t** previously have been prepared in 5 steps as inhibitors of liver X receptor-mediated cardiovascular disease.[9]

The combination of a silver salt and on water conditions was essential for successful arylation. Replacing Ag_2CO_3 with common inorganic bases such as alkali metal carbonates proved completely ineffective with water as solvent. Correspondingly, using acetonitrile in place of water under our reaction conditions gave poor yields of arylated indazoles (12% yield of **4o**, with 80% of starting indazole recovered). Sequestration of halide from the palladium catalytic cycle by Ag^+ appears pivotal to achieving arylation at 50 °C on water.

In summary, we have reported the first study of intermolecular direct arylation of indazoles. Using on water reaction conditions, a simple and efficient protocol has been developed that produces diverse C3-arylated indazoles under notably mild conditions.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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